



San Francisco VA Medical Center

## Research and Development Milestones



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# Preface

This is a compilation of selected research performed at the San Francisco Veteran Affairs Medical Center. It was prepared at the request of Secretary of Veterans Affairs, the Honorable James Nicholson, during his visit to SFVAMC in May of 2005. Research is a major reason for the high quality of care at the VA. SFVAMC has over 200 scientists; 80% are physician scientists and all are faculty members at the University of California, San Francisco. SFVAMC has the largest VA research program nationally. Our research program and academic affiliation allow for SFVAMC to recruit the best and brightest.

VA Research is Good Medicine.

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# Types of SFVAMC Research

## **Biomedical (Basic) Laboratory Research & Development**

Conducts research that explores basic biological or physiological principles in humans or animals but does not involve intact human beings. For example, it includes research on animal models and investigations of tissues, blood or other biologic specimens from humans.

## **Clinical Science Research & Development (Clinical)**

Conducts research that focuses on intact human beings as the unit of examination. Examples include interventional and effectiveness studies, clinical, epidemiological and technological studies. CSR&D is a new service created through a reorganization of the former Medical Research Service and Cooperative Studies Program.

## **Health Services Research & Development Service (HSR&D)**

HSR&D pursues research at the interface of health care systems, patients and health care outcomes. HSR&D underscores all aspects of VA health care; specifically quality, access, patient outcomes and health care costs. The HSR&D mission is to advance knowledge and promote innovations that improve the health and care of veterans and the nation. Many of the studies conducted by this Service have been used within and outside VA to assess new technologies, explore strategies for improving health outcomes, and evaluate the cost-effectiveness of services and therapies.



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## Basic

**Daniel D. Bikle, MD, PhD**

*Staff Physician, Medical Service, SFVAMC*

*Professor of Medicine and Dermatology, UCSF*

# Preventing Bone Loss and Investigating Skin Cancer

Skeletal unloading—when no stress is placed on the skeleton—occurs during prolonged bed rest, immobilization, and paralysis. It often leads to bone loss and resultant fractures. Dr. Bikle and his fellow researchers determined a likely cause of this bone loss: selective resistance to a growth factor called insulin-like growth factor (IGF-I), which is critical for normal bone growth and remodeling. They demonstrated that this resistance is linked, in turn, to a loss of expression of a major class of proteins, the integrins, which link the matrix of bone in which bone cells reside to the internal workings of those cells. They believe that efforts to restore or maintain the expression of these integrins should prevent the loss of IGF-I responsiveness during skeletal unloading. **This would prevent bone loss during periods of bed rest or immobilization, and protect our affected veteran population from fractures.**

Dr. Bikle also investigates skin cancer. This is the most common form of cancer, and represents a failure of the differentiation process in skin cells. Dr. Bikle found that both calcium and vitamin D regulate the development of major skin cells, and that furthermore, regulation of these substances within the skin cell may guard against the development of cancer. **Dr. Bikle and his associates anticipate that their studies may result in new methods to prevent the development of skin cancer in predisposed individuals, including those with excessive sun exposure, such as veterans returning from the Middle East.**

Sakata T, Wang Y, Halloran BP, Elalieh HZ, Cao J, Bikle DD. 2004. Skeletal unloading induces resistance to IGF-I by inhibiting activation of the IGF-I signaling pathways. *J Bone Min Res* 19:436-446.

Bikle DD. 2004. Vitamin D and skin cancer. *J Nutr* 134:3472S-3478S.



## Basic

**Lilly Y.W. Bourguignon, PhD**

*Career Scientist, Medical Service, SFVAMC*

*Professor of Medicine, UCSF*

# Cancer Cell Biology

Dr. Bourguignon is a cell biologist who has used a variety of biochemical, immunological and molecular biological techniques to elucidate the **role of the protein CD44 in regulating the progression of human solid tumors**, including breast cancer, ovarian cancer, prostate cancer, and head and neck squamous cell carcinoma. Her research studies also evaluate CD44 and various signaling molecules as **markers for the propensity of solid tumors to spread; such markers would aid in assessing prognosis and diagnosis**. Furthermore, she has developed several novel strategies to inhibit CD44-mediated signaling events and solid tumor progression. Her research could establish CD44 and associated signaling molecules as important tumor markers for **early detection and evaluation of cancer**, and could potentially allow the **development of new drugs**. Most importantly, the new information obtained from Dr. Bourguignon's cancer research program will have important clinical utility for the **diagnosis, prognosis, and treatment of veteran patients**, and therefore is highly relevant to the mission of SFVAMC.

Bourguignon LYW, Singleton P, Diedrich F, Stern R, Gilad E. 2004. CD44 Interaction with Na<sup>+</sup>/H<sup>+</sup> Exchanger (NHE1) creates acidic microenvironments leading to Hyaluronidase-2 & Cathepsin B activation and breast tumor cell invasion. *J Biol Chem* 279:26991-27007.

Bourguignon LYW, Gilad E, Rothman K, Peyrollier K. 2005. Hyaluronan-CD44 interaction with Cdc42-IQGAP1 promotes Cdc42 and ERK signaling leading to actin binding, ELK/estrogen receptor transcriptional activation and ovarian cancer progression. *J Biol Chem* 280:11961-11972.



## Basic

### James K. Brown, MD

*Staff Physician, Assistant Chief of Pulmonary/Critical Care Medicine, SFVAMC  
Associate Professor of Medicine, Cardiovascular Research Institute, UCSF*

# Scar Formation in Airways and Lungs

Dr. Brown focuses on the study of tryptase, an enzyme that is released from specific cells in the airways and lungs called mast cells. Several years ago, Dr. Brown and his fellow researchers discovered that tryptase has the capacity to make other cells, located near mast cells, grow and form scar tissue. Thus, tryptase causes scars to form around the airways in asthma and chronic obstructive pulmonary disease (COPD), leading to airflow obstruction that is irreversible and difficult to treat. Tryptase also causes scars to form in the lungs in patients with pulmonary fibrosis, thus making their lungs stiffer and causing shortness of breath. There is a need to develop medications that inhibit tryptase-induced scar formation. **The Brown laboratory is one of the few in the world working to understand how it is that tryptase causes scar formation so that such medications can be designed in a rational fashion.**

Brown JK, Jones CA, Rooney LA, Caughey GH. 2001. Mast cell tryptase activates extracellular-regulated kinases (p44/p42) in airway smooth-muscle cells: importance of proteolytic events, time course, and role in mediating mitogenesis. *Am J Respir Cell Mol Biol* 24:146-154.

Brown JK, Jones CA, Rooney LA, Caughey GH, Hall IP. 2002. Tryptase's potent mitogenic effects in human airway smooth muscle cells are via nonproteolytic actions. *Am J Physiol Lung Cell Mol Physiol* 282:197-206.



**George H. Caughey, MD**

*Staff Physician, Chief of Pulmonary/Critical Care Medicine, SFVAMC  
Professor of Medicine, UCSF*

# Preventing Lung Transplant Rejection & Investigating Mast Cells

Many veterans have end-stage lung diseases. For these veterans, the only current prospect for cure lies in receiving new lungs from a donor. However, the greatest barriers to survival and maintenance of a fully functioning graft are acute and chronic rejection. Rejection can be treated successfully. For this reason, Dr. Caughey and his colleagues are seeking more reliable ways to diagnose rejection. They have succeeded in developing an extremely sensitive technique for profiling gene expression in very small samples of tissue from the transplanted lung, and have identified specific gene products that correlate with rejection. **These studies they may lead to better diagnostic tests leading to improved diagnosis and management of rejection and better preservation of graft function in lung transplant recipients.** Plus, they improve our understanding of the lung's response to immunological attack and identify new and better targets for pharmaceutical prevention of rejection in veterans with transplanted lungs.

Dr. Caughey is perhaps best known for his work with mast cells, which play major roles in allergic diseases, including asthma and fatal reactions to bee stings. He has focused on mast cell proteases, which are enzymes that break down proteins. Over the past decade, Dr. Caughey's laboratory has developed several compelling lines of evidence to suggest that these proteases play deleterious roles in allergic diseases. **This work has resulted in pharmaceutical development of new classes of anti-inflammatory drugs to treat asthma and other diseases involving mast cells.**

Raymond WW, Ruggles Waugh S, Craik CS, Caughey GH. 2003. Albumin is a substrate of human chymase: Prediction by combinatorial peptide screening and development of a selective inhibitor based on the albumin cleavage site. *J Biol Chem* 278:34517-34524.

Xu X, Golden JA, Dolganov G, Jones KD, Donnelly S, Weaver T, Caughey GH. 2005. Transcript signatures of lymphocytic bronchitis in lung allograft biopsies. *J Heart Lung Transplant* (in press May 2005).



**Gary Cecchini, PhD**

*Senior Research Career Scientist, Chief of Molecular Biology, SFVAMC  
Research Biochemist, Department of Biochemistry and Biophysics, UCSF*

# Mitochondrial Biochemistry and Enzymology

**Dr. Gary Cecchini and colleagues were the first laboratory in the world to describe the three dimensional structure of Complex II (succinate dehydrogenase), a key member of the energy generating component of the mitochondrion, the “power plant” of the cell.** Their findings show how the architecture of this family of enzymes is arranged to lessen the formation of reactive oxygen species (ROS), which are thought to be important for diseases such as aging, neurodegeneration, and cardiac disease. Information derived from these structures has been the subject of numerous research articles which show how mutations of Complex II can contribute to tumor formation and neurodegeneration. The Cecchini laboratory is further studying how these mutations result in malfunction of Complex II and contribute to the disease process. **These studies show that the loss of enzyme function and the formation of ROS both contribute to processes that can contribute to cell death.**

Yankovskaya V, Horsefield R, Törnroth S, Luna-Chavez C, Miyoshi H, Léger C, Byrne B, Cecchini G, Iwata S. 2003. Architecture of succinate dehydrogenase and reactive oxygen species generation. *Science* 299:700-704.

Kotlyar AB, Maklashina E, Cecchini G. 2004. Absence of NADH channeling in coupled reaction of mitochondrial malate dehydrogenase and complex I in alamethicin-permeabilized rat liver mitochondria. *Biochem Biophys Res Commun* 318(4):987-91.

## Basic

**Thomas Chen, MD, PhD**

*Staff Physician, Medical Service, SFVAMC*

*Assistant Adjunct Professor of Medicine, UCSF*

# Signal Regulatory Proteins in Brain Tumors

Interest in **targeted therapies** for cancer has increased recently with the availability of compounds known as small molecule inhibitors. These inhibitors are not as toxic as standard chemotherapy; however, their effectiveness so far in treating brain tumors has been extremely limited and difficult to predict. Dr. Chren's studies focus on how these targeted therapies interact with a family of proteins called Signal Regulatory Proteins (SRPs), which appear to alter the signals that individual cells encounter upon stimulation with a variety of molecules, many of which are implicated in the cause of brain tumors. He has found that only 70 percent of brain tumors express SRPs, which may explain why these tumors do not respond in a consistent way to targeted therapies. His research continues to explore the mechanisms by which the SRPs modulate cancer signaling, and to further correlate his findings with clinical outcomes.

Chen TT, Brown EJ, Huang EJ, Seaman WE. 2004. Expression and activation of signal regulatory protein alpha on astrocytomas, *Cancer Res* 64:117-127.



## Basic

**Steven W. Cheung, MD**

*Staff Physician, Surgical Service, SFVAMC  
Associate Professor of Otolaryngology, UCSF*

# Treating Communication Disorders

Noise-induced hearing loss, tinnitus (ringing in the ear), and abnormalities in speech production are among some of the most common problems experienced by veterans and the general population. The overall goal of Dr. Cheung's research program is to **implement neurophysiologically-based treatment programs for patients with hearing and voice disorders**. Principles that guide clinical treatment programs are derived from animal studies. New treatment programs for patients are implemented using both established and newly-constructed learning systems. Dr. Cheung's laboratory also takes advantage of novel technologies such as transcranial magnetic brain stimulation, which uses electromagnetic pulses to induce electrical fields in the brain.

Godey B, Atencio CA, Bonham BH, Schreiner CE, Cheung SW. 2005. Functional organization of squirrel monkey primary auditory cortex: responses to frequency-modulation sweeps. *J Neurophysiol* 94(2):1299-1311.

Cheung SW, Nagarajan SS, Schreiner CE, Bedenbaugh PH, Wong A. 2005. Plasticity in primary auditory cortex of monkeys with altered vocal production. *J Neurosci* 25(10):2490-2503.



## Basic

**Rajvir Dahiya, PhD**

*Research Scientist, Medical Research Service, SFVAMC  
Professor of Urology, UCSF*

# Aging, Race, and Prostate Cancer

Dr. Dahiya's research focuses on ways to identify and characterize genes that are epigenetically (reversibly) silenced in **age-related prostate cancer**. These genes may be used for early diagnosis and prognosis of the disease. Another use is to identify possible genetic and epigenetic risk factors for race-related prostate cancer. In one study, Dr. Dahiya investigated whether over-expression of the genes cytochrome P450 1A1 and cytochrome P450 1B1 are risk factors for **race-related prostate cancer**. In another recent study, Dr. Dahiya reported that the tumor suppressor gene GSTP1 is inactivated at a significantly higher rate in African American prostate cancer patients than in Caucasian patients. These mechanisms provide us with **potentially novel approaches to the management of prostate cancer**.

Li L-C, Carroll PR, Dahiya R. 2005. Epigenetics changes in prostate cancer: implication for diagnosis and treatment. *J Natl Cancer Institute* 97:103-115.

Enokida H, Shiina H, Urakami S, Igawa M, Ogishima T, Pookot D, Li L-C, Tabatabai ZL, Kawahara M, Nakagawa M, Kane CJ, Carroll PR, Dahiya R. 2005. Ethnic group-related differences in CpG hypermethylation of the *GSTP1* gene promoter among African-American, Caucasian and Asian patients with prostate cancer. *Intl J Cancer* 116:174-181.



## Basic

**David I. Daikh, MD, PhD**

*Staff Physician, Medical Service, SFVAMC*

*Assistant Professor of Medicine, UCSF*

# Mechanisms of Autoimmune Disease

Many important diseases are caused by abnormal regulation of the immune system, resulting in tissue damage by a person's own immune system. Many of these autoimmune diseases affect veterans, including rheumatoid arthritis, multiple sclerosis, lupus and vasculitis. Dr. Daikh's research involves *in vivo* studies aimed at understanding the mechanisms underlying the pathogenesis of autoimmunity. In particular, this work has focused on the role of T cell activation in autoimmune responses. This work has shown costimulatory pathways can prevent the development and perpetuation of autoimmune disease in a mouse model for lupus. Current studies are examining the mechanism of this effect in normal and autoimmune mice, as well as determining whether this kind of intervention can result in tolerance to autoantigens. We are also studying the pathogenesis of autoimmune brain disease, which has direct implications for the treatment of lupus and multiple sclerosis. Another major emphasis is on the development of new therapeutic strategies using novel biologic agents for the treatment of lupus and other autoimmune disease. For example, **Dr. Daikh has shown that combining CTLA4Ig, a recombinant fusion protein that blocks T cell costimulation, with standard pulsed cyclophosphamide therapy results in a dramatic reversal of active lupus kidney disease in mice.** These studies have suggested a novel approach to using standard immunosuppressive therapies with newer biologic agents more safely and more effectively, and they have formed the basis for new clinical trials in humans with lupus.

Daikh DI, Wofsy D. 2001. Cutting Edge: Reversal of murine lupus nephritis with CTLA4Ig and cyclophosphamide. *Immunol* 166:2913-2916.

Cunnane G, Chan OTM, Cassafer G, Brindis S, Kaufman E, Yen BTS, Daikh DI. 2004. Prevention of murine lupus nephritis by CTLA4Ig and cyclophosphamide. *Arthritis and Rheumatism* 50:1539:1548.



## Basic

**Peter M. Elias, MD**

*Staff Physician, Dermatology Service, SFGVAMC*

*Professor of Dermatology, UCSF*

# Skin Surface Diseases, Abnormalities, and Treatments

Dr. Elias is working to determine how genetic abnormalities produce skin abnormalities in a group of inherited skin diseases, called the ichthyoses. Until recently, little was known about the pathogenesis (the link between the gene and clinical features) in each of these disorders. Working with collaborators worldwide, Dr. Elias has delineated the pathogenic basis for several of these diseases. Discovery of these mechanisms has led to new therapeutic approaches that promise to help affected patients, including veterans. Dr. Elias and his collaborators are also investigating causes and possible therapies for complications of Vaccinia vaccination, which could threaten individuals with atopic dermatitis with a risk for a life-threatening complication, eczema vaccinatum. **They have developed two animal models for atopic dermatitis and are beginning to assess a variety of potential corrective therapies for human patients.** Finally, Dr. Elias and his fellow investigators are studying the acidic surface of human skin, its protective functions, and how those functions are compromised by various disorders. This research project has led to several new patents related to novel approaches to the therapy and prevention of skin disorders. **These approaches may also result in improved treatment and prevention of complications in the aged veteran population.**

Elias, PM, et al. 2002. Basis for the permeability barrier abnormality in lamellar ichthyosis. *Exp Dermatol* 11: 248-256.

Behne, MJ, et al. 2002. NHE1 regulates stratum corneum permeability barrier homeostasis: microenvironment acidification assessed with FLIM. *J Biol Chem* 277: 47399-47406.



## Basic

**Kenneth Feingold, MD**

*Staff Physician, Medical Service, SFVAMC*

*Professor of Medicine, UCSF*

# Dietary Oxidized Cholesterol and Atherosclerosis

Atherosclerosis (arterial plaque) remains a major cause of death in the US. Both heredity and environmental factors are associated with an increased risk of atherosclerosis. Previous studies have demonstrated that oxidized fats in the diet, including cholesterol, accelerate atherosclerosis in various animal models, there is abundant evidence that the American diet contains large quantities of these fats. Dr. Feingold's research has been directed toward understanding how the presence of these dietary fats influence the atherosclerotic process. He plans to study the mechanisms by which dietary oxidized cholesterol is absorbed by the small intestine, the pathways by which it is incorporated into LDL cholesterol, and its effects on atherosclerosis. **Dr. Feingold's results will provide a basis for modification of diets to minimize oxidized cholesterol in the diet, and may point to strategies for developing medications to decrease its effects.**

Staprans I, Pan XM, Rapp JH, Grunfeld C, Feingold KR. 2000. Oxidized cholesterol in the diet accelerates the development of atherosclerosis in LDL receptor- and apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol* 20(3):708-14.

Staprans I, Pan XM, Rapp JH, Feingold KR. 2003. Oxidized cholesterol in the diet is a source of oxidized lipoproteins in human serum. *J Lipid Res* 44(4):705-15.



## Basic

### Bernard Halloran, PhD

*Research Career Scientist, Medical Service, SFVAMC*

*Professor of Medicine, UCSF*

# Causes and Possible Prevention of Osteoporosis

Dr. Halloran is one of handful of scientists whose work is focused **on cell aging and age-related osteoporosis**, a disease in which bone is gradually lost with advancing age, leading to painful and debilitating hip and spine fractures. Normally, bone is in balance, continually formed and then torn down. This process is regulated by two proteins, RANKL, which tears bone down, and OPG, which helps preserve bone. Dr. Halloran has shown that as the **cells in bone age, they make too much RANKL and not enough OPG**. This causes bone to be lost and patients to develop osteoporosis. Work is now focused on why the aging cells of bone produce too much RANKL. Drugs to reduce RANKL production or increase OPG production could reduce age-related bone loss and prevent osteoporosis.

Cao J, Venton L, Sakata T, Halloran BP. 2003. Expression of RANKL and OPG correlates with age-related bone loss in male C57BL/6 mice. *J Bone Min Res* 18(2):270-277.



## Basic

### Walter M. Holleran, PharmD

*Research Chemist, Dermatology Service, SFVAMC*

*Associate Adjunct Professor of Dermatology and Pharmaceutical Chemistry, UCSF*

# Improving the Skin Barrier

The protective barrier of human skin is embedded in a lipid matrix consisting of cholesterol, fatty acids, and a unique class of nitrogen-containing lipids called ceramides. Many skin diseases that affect both veterans and the general population have alterations in the normal pattern of cells and/or lipid layers. **Dr. Holleran has defined many of the biochemical processes that allow for normal skin barrier function to develop and persist.** His current work, in collaboration with other SFVAMC researchers, explores mechanisms that protect the critical outer skin layers against oxidative stress insults, such as those due to ultraviolet light exposure. After these insults, large quantities of ceramide lipids are produced, which in turn threatens skin cells with premature cell death, called apoptosis. Dr. Holleran's team has defined two enzymatic pathways that protect the outer skin layers from oxidative stress. In addition, Dr. Holleran's recent collaborative efforts have revealed a critical role for a gene family, called the 'grainyhead-like' Grhl genes, in the formation and healing of the normal protective skin barrier. **These mechanisms could be exploited to develop novel therapies for a number of skin disorders, including atopic dermatitis, which affects approximately 10 percent of the veteran population.**

Uchida Y, DiNardo A, Elias PM, Holleran WM. 2003. De novo synthesis of ceramide mediates Ultraviolet B irradiation-induced apoptosis in cultured human keratinocytes. *J Invest Dermatol* 120:662-9.

Ting SB, Caddy J, Hislop K, Wilanowski T, Auden A, Zhao L, Ellis S, Kaur P, Uchida Y, Elias PM, Holleran WM, Cunningham JM, Jane SM. 2005. Mouse *Grhl3*, a homolog of Drosophila grainyhead, is essential for surface barrier formation and wound healing. *Science* 308:411-413.



## Basic

**Eric J. Huang, MD, PhD**

*Staff Physician, Pathology Service, SFVAMC  
Associate Professor of Pathology, UCSF*

# How Sensory Neurons Die and How to Prevent Sensory Neuronal Death

Research in Dr. Huang's lab has shown that in the mouse sensory nervous system, too **much of the transcription cofactor HIPK2 causes cell death**, and reducing HIPK2 reduces cell death. It is well-established that hypoxia (lack of oxygen), toxins, traumatic injuries, and medical illnesses often result in irreversible damage to the sensory and autonomic nervous systems. However, there has been a lack of effective therapeutic means that might prevent or cure these debilitating conditions. Given the important role of HIPK2 in regulating cell death, one future direction is to explore the mechanisms that regulate HIPK2 activity. Dr. Huang is in the process of modifying HIPK2 at the genomic level to create mouse mutants that would allow for screening drugs or chemicals that could inhibit HIPK2 activity.

Wiggins AK, Wei G, Doxakis E, Wong C, Tang AA, Zang K, Luo EJ, Neve RL, Reichardt LF, Huang EJ. 2004. Interaction of Brn3a and HIPK2 mediates transcriptional repression of sensory neuron survival. *J Cell Biol* 167:257-67.

Huang EJ, Li H, Tang AA, Wiggins AK, Neve RL, Zhong W, Jan LY, Jan YN. 2005. Targeted deletion of numb and numlike in sensory neurons reveals their essential functions in axon arborization. *Genes Dev* 19(1):138-151.



## Basic

**Millie Hughes-Fulford, PhD**

*Scientific Advisor to the Under Secretary  
of the Department of Veterans Affairs, SFVAMC  
Adjunct Professor of Medicine, UCSF*

# Diet Intervention in Treatment of Prostate Cancer & Loss of Immune Response in Space

**Dr. Error! Reference source not found.** has published research indicating that human tumors in mice fed diets high in omega-6 fatty acids have increased levels of cox-2 and cPLA2, proteins known to be responsible for increased prostate tumor growth. Moreover, she has shown that these proteins are inhibited by flurbiprofen, which targets cPLA2. This suggests a potential alternative cancer therapy to cox-2 inhibitors, which have cardiovascular complications. In upcoming studies, Drs. Hughes-Fulford and Chris Kane (Chief of Urology, SFVAMC) will investigate the effect of dietary fatty acids on stage and growth of prostate cancer in human patients. **The results from these upcoming studies will help in the development of dietary guidelines for future and current prostate cancer patients.**

Dr. Hughes-Fulford is also the only VA scientist-astronaut to go into space. The physical mechanisms by which the T-cell—an essential component of the immune system—responds to gravity remain an intriguing enigma, and the Space Shuttle and International Space Station offer abundant opportunities for future studies. Dr. Hughes-Fulford identified the genes induced during a normal immune response, and has shown that it is highly likely that zero gravity affects these genes in a way that prevents T-cell activation. **Such studies will advance our understanding of the human immune system in health and disease and give us insight into the fundamental biological laws governing Earth's gravity-based life.**

Hughes-Fulford M, Chen Y, and Tjandrawinata RR. 2001. Fatty acid regulates gene expression and growth of human prostate cancer PC-3 cells. *Carcinogenesis* 22:701-7.

Hughes-Fulford M, Tjandrawinata RR, Li CF, Sayyah S. 2005. Arachidonic acid, an Omega-6 fatty acid, induces cytoplasmic phospholipase A2 in prostate carcinoma cells. *Carcinogenesis* (Epub ahead of print).



## Basic

**Gary Jarvis, PhD**

*Research Microbiologist, Medical Service, SFVAMC  
Associate Adjunct Professor of Laboratory Medicine, UCSF*

# Preventing Secondary Infections in Persons with HTLV-II

An estimated 200,000 persons in the United States are infected with human T lymphotropic virus type II (HTLV-II). In addition to the primary viral infection, the virus has been linked to an increased incidence of bacterial pneumonia. To determine whether HTLV-II infection is associated with an impaired immune system, Dr. Jarvis and his team immunized a group of HTLV-II-infected subjects and a group of matched uninfected control subjects with vaccines for pneumococcal pneumonia and tetanus. The research revealed that the subjects infected with HTLV-II responded positively to both vaccines. **This is significant because it demonstrated that vaccines may offer them protection against infections for which they are at high risk, including pneumonia and influenza.**

Jarvis GA, Janoff EN, Cheng H, Devita D, Fasching C, McCulloch CE, Murphy EL. 2005. Human T lymphotropic virus type II infection and humoral responses to pneumococcal polysaccharide and tetanus toxoid vaccines. *J Infect Dis* 191:1239-1244.



## Basic

**Joel S. Karliner, MD**

*Staff Physician, Medical Service, SFVAMC*

*Professor of Medicine, UCSF*

# Investigating New Strategies for Protection Against Heart Damage

Dr. Karliner uses models of heart disease in rodents to study the effects of drugs and of the body's natural defenses, with the goal of understanding how these drugs and defenses might be used to prevent acute heart attacks. These models simulate acute heart attack through either oxygen deprivation or abrupt cessation of blood supply to the heart in order to determine the functional and biochemical effects of these interventions. Effects of drugs and natural defenses are investigated in heart tissue, isolated heart cells, and mitochondria, which generate energy within cells. These studies also include the use of genetically altered mice in which one gene is deleted or excessively active, in order to discover how these genes and the proteins that are derived from them are involved in the mechanisms of protection against heart attack. New knowledge about the mechanism of action of these drugs and defenses, and how they affect biochemical signals and enzymes, can lead to **new strategies that would either prevent or ameliorate heart damage in patients undergoing a variety of procedures**. These procedures include both cardiac and noncardiac surgery in patients, especially elderly veterans, who are at higher risk for heart damage during and after stressful procedures. Patients undergoing stent deployment in coronary arteries and other vessels will also benefit.

Zhu B-q, Zhou H-z, Teerlink JR, Karliner JS. 2004. Pyrroloquinolone (PQQ) decreases myocardial infarct size and improves cardiac function in rat models of ischemia and ischemia/reperfusion. *Cardiovascular Drugs and Therapy* 18:421-431.

Jin Z-Q, Goetzl EJ, Karliner JS. 2004. Sphingosine kinase activation mediates ischemic preconditioning in murine heart. *Circulation* 110:1980-1989.



## Basic

**Hubert T. Kim, MD, PhD**

*Staff Physician, Surgical Service, SFGVAMC  
Associate Professor of Orthopedic Surgery, UCSF*

# Preventing Joint Injuries by Preventing Programmed Cell Death

Dr. Kim was the first researcher to report an association between fractures of the knee joint and a form of programmed cell death termed apoptosis. Blocking apoptosis has been proposed as a potential therapeutic approach to treat injuries involving joint cartilage. His subsequent research has demonstrated that inhibitors of enzymes critical to the process of apoptosis can decrease cartilage degeneration after joint injuries in animals. Ongoing studies will determine whether treatment with these types of enzyme inhibitors can decrease the chances of developing arthritis for patients who have sustained severe knee injuries.

Kim HT, Lo MY, Pillarisetty R. 2002. Chondrocyte apoptosis following intra-articular fracture in humans. *Osteoarthritis and Cartilage* 10(9):747-9.

Coustouros JG, Dang AC, Kim HT. 2003. Inhibition of chondrocyte apoptosis *in vivo* following osteochondral injury. *Osteoarthritis and Cartilage* 11(10):756-759.

## Basic

### Corey Largman, PhD

*Career Scientist, Medical Research Service, SFVAMC  
Professor of Medicine and Dermatology, UCSF*

# Expansion of Hematopoietic Adult Stem Cells & the Role of HOX Genes in Leukemia

Dr. Largman and colleagues were the first to demonstrate that addition of the HOXB4 homeobox gene to bone marrow cells led to the efficient and specific expansion of stem cells. **This finding, which was the subject of a US Patent, has substantial implications for bone marrow transplantation in several patient populations.** Since Dr. Largman's pioneering work, other research groups have built on these studies to demonstrate that merely adding the HOXB4 protein to the media in which the cells are grown can expand human adult bone marrow stem cells in a dish, prior to transplantation. A number of laboratories are currently planning clinical trials to examine the effectiveness of stem cell expansion using technologies based on these original findings.

In related research, Dr. Largman's lab was among the first groups to show that the HOX genes regulate aspects of normal bone marrow cell differentiation. Leading from this discovery, he and others have shown that inappropriate production of the HOXA9 protein appears to play a central role in many acute leukemias. Current research is directed towards developing strategies to turn off the HOXA9 gene or to destroy the HOXA9 protein in the leukemic cells from patient bone marrow samples and from experimental leukemias in mice. **Dr. Largman has demonstrated that turning off HOXA9 can prevent the growth of leukemic cells in culture.**

Sauvageau G, Thorsteinsdottir U, Eaves CJ, Lawrence HJ, Largman C, Lansdorp PM, Humphries RK. 1995. Overexpression of HOXB4 in hematopoietic cells causes the selective expansion of more primitive populations in vitro and in vivo. *Genes & Dev* 9:1753-1765.

Vijapurkar U, Fischbach N, Shen W-F, Brandts C, Stokoe D, Lawrence HJ, Largman C. 2004. Protein Kinase C-mediated phosphorylation of the leukemia-associated HOXA9 protein impairs its DNA binding ability and induces myeloid differentiation. *Mol Cell Biol* 24:3827-3837.



## Basic

**Yun-Fai Chris Lau, PhD**

*Research Career Scientist, Medical Service, SFVAMC*

*Professor of Medicine, UCSF*

# Links Between the Y Chromosome and Disease

Dr. Lau is an established and internationally recognized molecular geneticist, particularly in the fields of the Y chromosome field and male-specific disorders. For the past 25 years, his research has focused on understanding the molecular causes for a diverse spectrum of human diseases, and **designing therapeutic strategies** for those diseases. Current efforts, funded by the Department of Defense among other sources, are directed in two general areas: 1) the role of the Y chromosome in male-specific cancers, gonadal dysgenesis, male hypertension and cardiovascular dysfunction, and 2) the effects of structural abnormalities in mitochondria (the “power plant” of the cell) in oxidative stress, cancer, neurodegeneration, Alzheimer’s, and cardiovascular diseases. **Outcomes of his research have provided significant insights in understanding the causes of, and offer potential diagnoses and therapies for, human diseases, many of which affect millions of our aging veterans.**

Lau Y-FC, Lau H, Kömüves LG 2003. Expression pattern of a gonadoblastoma candidate gene suggests a role of the Y chromosome in prostate cancer. *Cytogenet Genome Res* 101:250-260.

Kido T, Lau YF. 2005. A Cre gene directed by a human TSPY promoter is specific for germ cells and neurons. *Genesis* 42:263-75.



## Basic

### H. Jeffrey Lawrence, MD

*Staff Physician, Medical Service, SFVAMC*

*Professor of Medicine, UCSF*

# HOX Genes in Disease and Health

Dr. Lawrence's laboratory pioneered the study of a certain family of genes, known as homeobox (HOX) genes, in blood formation. His research has shown that **HOX genes are important for normal blood development**, but that abnormal expression of HOX genes can lead to leukemia. He is currently studying how these genes work to produce normal blood cells. He is also studying ways to **block the function of these genes as a potential treatment of leukemia**. In addition, he is studying **the expression of HOX genes in prostate cancer**, a very common malignancy in our veteran population. Lastly he is interested in **using HOX proteins to expand stem cells** from the blood, skin and other tissues to use for transplantation purposes to treat blood disorders, burns and other medical problems.

Schneider TE, Barland C, Alex AM, Mancianti ML, Lu Y, Cleaver JE, Lawrence HJ, Ghadially R. 2003. Measuring stem cell frequency in epidermis: a quantitative in vivo functional assay for long-term repopulating cells. *Proc Natl Acad Sci USA* 100:11412-11417.

Fischbach NA, Rozenfeld S, Shen W-F, Fong S, Chrobak D, Ginzinger D, Kogan SC, Radhakristnan A, Le Beau MM, Largman C, Lawrence HJ. 2005. HOXB6 overexpression in murine bone marrow immortalizes a myelomonocytic precursor *in vitro* and causes hematopoietic stem cell expansion and acute myeloid leukemia *in vivo*. *Blood* 105:1456-1466.



**Michael J. Mann, MD**

*Staff Physician, Surgical Service, SFVAMC*

*Assistant Professor of Surgery, UCSF*

## Cellular and Molecular Therapies for Cardiovascular Disease

**The Cardiothoracic Translational Research Laboratory is focused on turning a deeper understanding of the complex biology of failing heart cells into a new generation of cellular and molecular therapies that may actually reverse the ravages of heart failure.** This lethal condition affects more than 5 million Americans and is already the greatest single economic burden in American health care, yet no existing therapies can either halt or reverse the disease process. Dr. Mann's group is analyzing the molecular basis of the failing heart's response to non-embryonic stem cell transplantation, and these results will provide a framework for the first rational design of optimized strategies for human cardiac stem cell therapy. His group also works closely with the SF VA Cardiac Biomechanics Laboratory, headed by Drs. Mark Ratcliffe and Julius Guccione, which has developed among the world's most advanced computerized mathematical programs that can model and predict the biophysics of cardiac function. Together, they are applying these capabilities to better understand both cell transplantation, as well as the emerging field of surgical reconstruction of damaged hearts. In addition, Dr. Mann collaborates with Dr. Kevin Healy and other bioengineers from the UC Berkeley campus to apply novel artificial materials toward both the delivery of non-embryonic stem cells to intact hearts and the engineering of bioartificial heart tissue.

Mann MJ, Dzau VJ. 2002. Molecular approaches for the treatment of atherosclerosis. *Card Clin* 20:1-11.

Nicholas S, Mishell J, Cha J, Honbo N, Jin Z, Karliner J, Mann MJ. PI3K Signaling and the Development of a Hybrid Molecular and Surgical Approach to Post-MI Heart Failure. Keystone Symposium, Molecular Biology of Cardiac Disease and Regeneration, April 3-8, 2005.

## Basic

**Gerald B. Matson, PhD**

*Facilities Manager, MR Unit, SFVAMC*

*Adjunct Professor of Pharmaceutical Chemistry, UCSF*

# Designing Improved Methods for Human Brain Spectroscopy

Dr. Matson's work has been directed toward developing improved methods to measure human brain metabolites—products of brain metabolism—by using magnetic resonance spectroscopy (MRS). **The goal of this work is better, more accurate diagnosis of brain diseases.** As part of this effort, he has been developing computer simulation methods to improve current MRS techniques. Recently, he developed improved methods to preserve metabolite signals that normally decay rapidly, making them difficult to quantify. **This work should lead to more accurate signal measurement of brain metabolites, including myo-inositol, which has been observed at higher levels in persons with Alzheimer's disease, and glutamate, a neurotransmitter whose level may be altered in a variety of brain diseases.**

Maudsley AA, Govindaraju V, Young K, Aygula ZK, Pattany PM, Soher BJ, Matson GB. 2005. Numerical simulation of PRESS localized MR spectroscopy. *J Magn Reson* 173:54-63.

Soher BJ, Pattany PM, Matson GB, Maudsley AA. 2005. Observation of coupled 1H metabolite resonances at long TE. *Magn Reson Med* 53:1283-87.



## Basic

### Theodora Mauro, MD

*Staff Physician, Chief of Dermatology, SFVAMC*

*Associate Professor in Residence and Vice Chair of Dermatology, UCSF*

# Skin Acidification

**Dr. Mauro was the first researcher to identify specific pumps in skin cells that acidify the uppermost region of skin and allow the skin to form a protective barrier.** If this barrier is damaged, skin becomes dry and itchy, and common conditions, such as eczema, become much worse. Dr. Mauro has found that these pumps are important for newborn skin to acidify itself after birth. In addition, these pumps seem to be less active in aged skin, possibly causing or exacerbating skin diseases commonly seen in the aging veteran population. Dr. Mauro has developed a new approach to study skin condition, fluorescence lifetime imaging, which allow researchers to see exactly where and how fast skin acidifies itself. **These studies will help in the development of topical agents that might hasten skin barrier recovery, via optimum skin acidification, in infants and adults.**

Behne MJ, Meyer JW, Hanson KM, Barry NP, Murata S, Crumrine D, Clegg RW, Gratton E, Holleran WM, Elias PM, Mauro TM. 2002. NHE1 regulates the stratum corneum permeability barrier homeostasis. Microenvironment acidification assessed with fluorescence lifetime imaging. *J Biol Chem* 277(49):47399-406.

Behne MJ, Barry NP, Hanson KM, Aronchik I, Clegg RW, Gratton E, Feingold K, Holleran WM, Elias PM, Mauro TM. 2003. Neonatal development of the stratum corneum pH gradient: localization and mechanisms leading to emergence of optimal barrier function. *J Invest Dermatol* 120(6):998-1006.



## Basic

**William S. McIntire, PhD**

*Research Chemist, Medical Research Service, SFVAMC*

*Research Biochemist, Department of Molecular Biology, UCSF*

# Probing Cell Biochemistry to Better Understand and Treat Disease

Dr. McIntire works to develop treatments for cancer. He employs computer molecular modeling of protein structures, computer-aided drug design, sophisticated kinetic methodologies, modern molecular biological techniques, cell biology and physiology, and the use of animal models. His research focuses on enzymes containing special cofactors, which are substances that certain enzymes need to carry out their reactions. **This work will contribute to a better understanding of human enzymes and their participation in diseases.** Dr. McIntire is also very interested in the medical and pharmacological importance of human polyamine oxidase (PAO), a protein involved in cell metabolism. He was the first to clone and sequence the gene for PAO and to obtain pure enzyme for biochemical and pharmacological studies. His research group was the first to determine how PAO is inhibited by a well-known drug. These efforts will result in a better understanding of fundamental cellular processes such as cancer, cell death, oxidative stress, tissue damage, tissue differentiation and development, and wound healing. **Dr. McIntire's research sets a solid foundation for the development of new therapeutic agents to treat cancer, heart disease, asthma, traumatic and ischemia/reperfusion injuries (e.g., stroke), and other human maladies.**

Wu T, Yankovskaya V, McIntire WS. 2003. Cloning, Sequencing, and Heterologous Expression of the Murine Peroxisomal Flavoprotein, N 1-Acetylated Polyamine Oxidase. *J Biol Chem* 278:20515-25.

Wu T, Ling K-Q, Sayre LM, McIntire WS. 2005. Inhibition of Murine N 1-Acetylate Polyamine Oxidase by an Acetylenic Amine and the Allenic Amine, MDL 72527. *Biochem Biophys Res Commun* 326:483-490.



## Basic

**James H. McKerrow, MD, PhD**

*Staff Physician, Anatomic Pathology Service, SFVAMC*

*Professor of Cell and Molecular Pharmacology and Pathology, UCSF*

# New Drugs For Parasitic Diseases of the Developing World

Diseases caused by parasites, including leishmaniasis, schistosomiasis, and malaria, represent major global health problems and affect literally billions of people. Despite the global burden of these parasitic infections, there are no vaccines and few drugs to treat or prevent the diseases that they produce. Many of our World War Two veterans contracted schistosomiasis and malaria in the Pacific theater. **Today, parasitic diseases are major problems for veterans of the Iraq and Gulf wars—particularly leishmaniasis, known to returning vets as “Baghdad Boil.”** To fill the research gap, Dr. McKerrow and colleagues organized an unusual interdisciplinary consortium—the Tropical Disease Research Unit—with the goal of fashioning the equivalent of a drug company research effort within an academic setting. **The consortium has had two recent successes: completion of preclinical development of a drug for Chagas’ disease, the leading cause of heart disease in Latin America, and the identification of up to 90 potential drug treatments for leishmaniasis.** Information about these potential treatments is being disseminated throughout the worldwide medical community. Because these drugs are already approved for human use, their “pipeline” to patients has the potential to be significantly shorter than is typical for new drugs.

Mahmoudzadeh-Niknam H, McKerrow JH. 2004. Leishmania tropica: cysteine proteases are essential for growth and pathogenicity. *Exp Parasitol* 106(3-4):158-63.

Debnath A, Das P, Sajid M, McKerrow JH. 2004. Identification of genomic responses to collagen binding by trophozoites of *Entamoeba histolytica*. *J Infect Dis* 190(3):448-57.



## Basic

**Dieter J. Meyerhoff, Dr.rer.nat.**

*Senior Researcher, Radiology Service, SFVAMC*

*Professor of Radiology, UCSF*

# Brain GABA and Glutamate in Acute PTSD

**Chronic combat-related post traumatic stress disorder (PTSD) is present in 11 to 17 percent of Iraq and Afghanistan veterans, and often accompanied by alcohol and other substance abuse, depression, difficulties with interpersonal relationships, poorer occupational history, and increased physical health problems.** SFVAMC recently obtained a high-field magnetic resonance MR scanner (4 Tesla), the only one of its kind in the VA system. Dr. Meyerhoff will use its capability of measuring neurotransmitters such as GABA and glutamate in returning Iraqi veterans with and without combat-related PTSD. These brain chemicals are critical for registration and encoding of emotions and fear. Their imbalance, long-lasting dysfunction, and related cell death are thought to explain the clinical symptomatology of stress-related anxiety disorders, including PTSD, but the relationship between blood and brain GABA levels is unknown. In addition, **the potential effects of alcohol use, depression, anxiety, and smoking on neurotransmitter levels will be investigated.** Some patients will also participate in a study on D-Cycloserine, a potential new treatment for PTSD, and will be studied by high-field MR spectroscopy before and after treatment.

Gazdinski S, Durazzo TC, Meyerhoff DJ. 2005. Temporal dynamics and determinants of whole brain tissue volume changes during recovery from alcohol dependence. *Drug Alcohol Depend* 78(3):263-73.



## Basic

**Robert A. Nissenson, PhD**

*Senior Research Career Scientist, Medical Research Service, SFVAMC  
Professor of Medicine and Physiology, UCSF*

# Cancer and Excess Blood Calcium

Dr. Nissenson and his colleagues have newly identified **a factor produced by tumors that is responsible for the syndrome of malignancy-associated hypercalcemia, or excess blood calcium—a common and serious side effect of a variety of cancers.** The factor that produces this syndrome is parathyroid hormone-related protein (PTHrP). Many tumors produce large amounts of this protein, which circulates in the bloodstream and reproduces the biological effects of parathyroid hormone on bone and kidney, resulting in high blood calcium levels. Dr. Nissenson and his colleagues also developed and validated an assay for the **measurement of this factor in human blood samples**, permitting physicians to readily distinguish hypercalcemia due to malignancy from hypercalcemia due to excess parathyroid hormone (hyperparathyroidism).

Strewler GJ, Stern PH, Jacobs JW, Eveloff J, Klein RF, Leung SC, Rosenblatt M, Nissenson RA. 1987. Parathyroid hormone-like protein from human renal carcinoma cells: structural and functional homology with parathyroid hormone. *J Clin Invest* 80:1803-1807.

Budayr AA, Nissenson RA, Klein RF, Pun KK, Clark OH, Diep D, Arnaud CD, Strewler GJ. 1989. Increased serum levels of a parathyroid hormone-like protein in malignancy associated hypercalcemia. *Ann Intern Med* 111:807-812.



## Basic

**Dennis H. Oh, MD, PhD**

*Staff Physician, Assistant Chief of Dermatology, SFVAMC*

*Assistant Professor of Dermatology, UCSF*

# Mechanisms and Therapy for Skin Cancers

Cancers of the skin are the most common cancers in the United States as well as in the veteran population. **Dr. Oh's interests are to understand and ultimately to manipulate the response of the skin to cancer-causing agents.** His laboratory has discovered that skin cells possess unique responses to solar radiation-induced DNA damage; for example, unlike other cells, skin cells efficiently continue to repair DNA damage from ultraviolet light even if they lack a protein known as p53. His laboratory has begun to identify the molecular mechanisms that govern repair in skin cells and that may be important future pharmacologic targets for the prevention and treatment of skin cancers. Dr. Oh's laboratory is also developing novel methods for targeting DNA damage precisely while sparing surrounding cells. These approaches have been combined with methods his laboratory has developed for targeting specific genes that are involved in skin cancer metastasis. **These methods may lead to non-surgical treatments for skin cancers that eliminate cancer cells while leaving normal cells unharmed.**

Oh DH, King BA, Boxer SG, Hanawalt PC. 2001. Spatially localized generation of nucleotide sequence-specific DNA damage. *Proc Natl Acad Sci USA* 98:11271-11276.

Oh DH, Yeh K. 2005. Differentiating human keratinocytes are deficient in p53 but retain global nucleotide excision repair following ultraviolet radiation. *DNA Repair* (Epub ahead of print).



## Basic

**S. Scott Panter, PhD**

*Research Chemist/Physiologist, Neurology Service, SFVAMC  
Adjunct Assistant Professor of Neurological Surgery, UCSF*

# Protecting Against Stroke with Intranasal Deferoxamine

**Dr. Panter and his colleagues were the first research group in the VA system to deliver drugs directly to the brain by an intranasal route, bypassing the blood-brain barrier in a non-invasive method.** They chose a specific drug for these studies: deferoxamine (DFO), which is FDA-approved for the treatment of acute iron poisoning and chronic, transfusion-related iron overload. It is usually administered systemically but does not readily enter the brain; therefore, they decided to utilize intranasal delivery. They selected a pretreatment model because a specific surgical procedure, coronary artery bypass graft (CABG) surgery, is performed on thousands of veterans annually; however, it is also a procedure that can result in an outcome of significant neurological dysfunction, including stroke and cognitive impairment. They found that brain damage from stroke was reduced 65% in animals treated with intranasal DFO 48 hours prior to stroke. **These data suggest that, in the future, patients scheduled to undergo CABG surgery may be able to reduce adverse neurological outcome by using a nasal sprayer to self-administer DFO prior to surgery.**

Panter SS, Coppes VG, Ferrell CM, Chavez JC, Ratan RR, Frey II WH. 2004. Intranasal Deferoxamine protects against subsequent stroke. 2004. Program No. 456.15. Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, Online.



## Basic

### Lynn Pulliam MS, PhD

*Associate Chief of Staff for Research and Chief of Microbiology, SFVAMC  
Professor of Laboratory Medicine and Medicine, UCSF*

# HIV Dementia

Dr. Pulliam' laboratory was the **first to show that blood monocytes (white blood cells) from individuals with HIV release “toxins” that kill or damage neurons in the brain.** This finding demonstrated that the dementia associated with HIV infection was not caused by direct HIV infection of brain cells but rather the immune cells themselves. This changed the way scientists looked at HIV infection of the brain.

Dr. Pulliam further reported that a subset of blood monocytes, called CD69, released this “toxin,” which in turn caused brain cells to turn on genes in the brain to program themselves for death. There was a substantial increase in CD69 monocytes from individuals with HIV dementia that was not seen in patients with AIDS alone or control HIV negative individuals. In a follow-up study, CD69 was elevated in individuals with Alzheimer's disease, indicating that **this monocyte subset could be predictive of dementia as well as a target for therapeutics for dementia.**

Dr. Pulliam and her fellow researchers recently reported that Tat, a protein secreted by HIV, inhibits neprilysin, the major protein that degrades amyloid beta (Abeta). Abeta accumulation is thought to be an early event in Alzheimer's disease. She looked at brains from autopsies of individuals with HIV dementia and **saw an increase in Abeta associated with those individuals who had been HIV infected the longest.** All individuals were on antiretroviral therapy. This suggests that while individuals with HIV now live longer, they **run an increased risk of developing an Alzheimer's-like dementia.**

Pulliam L, Herndier BG, Tang NM, McGrath MS. 1991. Human immunodeficiency virus-infected macrophages produce soluble factors that cause histological and neurochemical alterations in cultured human brains. *J Clin Invest* 87:503-12.

Pulliam L, Gascon R, Stubblebine M, McGuire D, McGrath MS. 1997. Unique monocyte subset in patients with AIDS dementia. *Lancet* 349:692-5.

Rempel H, Pulliam L. 2005. HIV-1 Tat inhibits neprilysin and elevates amyloid beta. *AIDS* 19:127-135.

## Basic

**Robert L. Raffai, PhD**

*Assistant Research Scientist, Surgical Service, SFVAMC*

*Assistant Adjunct Professor of Surgery, UCSF*

# Diabetes and Peripheral Arterial Disease

Peripheral arterial disease (PAD) is caused by fatty blockages, called atherosclerosis, in arteries throughout the body, including in the arms, neck, and legs. PAD normally occurs in the elderly, causing leg pains that limit walking. Advanced PAD often requires amputation of feet, and operations to prevent death from kidney failure, heart failure, and stroke. Diabetes is a major risk factor for PAD, causing atherosclerosis to develop early in life in peripheral arteries very close to limbs. How and why this occurs, and whether high blood sugar (hyperglycemia) is responsible, is not known. The lack of genetically engineered mouse models of PAD has severely blocked research aimed at understanding how diabetes accelerates PAD. Dr. Raffai **recently developed a mouse model of PAD**. In these mice, PAD develops naturally because of high blood lipids. However, a genetic switch allows Dr. Raffai to lower their blood lipids and reverse atherosclerosis. This unique PAD mouse will be used to test if and how hyperglycemia can cause premature PAD. Genetic analysis will be used to study how hyperglycemia causes atherosclerosis to develop in arteries close to limbs and organs. Lastly, research will be done to test if hyperglycemia can block the reversal of atherosclerosis, and if insulin treatment can overcome this block. **Results from these studies will provide valuable new knowledge to help fight PAD**, a devastating and tragic disorder frequently affecting our growing population of veterans who suffer from diabetes.

Raffai RL, Loeb SM, Weisgrabe KH. 2005. Apolipoprotein E promotes the regression of atherosclerosis independently of lowering plasma cholesterol levels. *Arterioscler Thromb Vasc Biol* 25: 436-441.



## Basic

### Joseph Rapp, MD

*Staff Physician, Chief of Vascular Surgery Service, SFVAMC  
Professor of Surgery, UCSF*

# Investigating Causes of Vascular Dementia

Vascular dementia is recognized as a common cause of intellectual deterioration in the elderly. While it can occur after stroke, it is also thought to occur as the result of lesions in the brain caused by hypertension. However, microemboli (tiny blood clots) in the brain, originating from the heart or carotid arteries, cause lesions similar to those occurring from hypertension. Microemboli frequently occur in the elderly population and Dr. Rapp hypothesizes that these are an unrecognized cause of vascular dementia. **His research has shown that microemboli cause small breaks in the blood-brain barrier, initiate an inflammatory response in the brain, and start a potentially destructive immune response as well.** These data suggest that imaging tests such as transcranial Doppler could be used to identify patients at risk for microembolization and to determine the need for aggressive preventive therapy.

Rapp JH, Pan XM, Sharp FR, Shah DM, Wille GA, Velez PM, Higashida RT, Saloner D. 2000. Atheremboli to the brain: Size threshold for causing acute neuronal cell death. *J Vasc Surg* 32:68-76.

Rapp JH, Pan XM, Yu B, Swanson RA, Higashida, RT, Simpson P, Saloner D. 2003. Cerebral ischemia and infarction from atheroemboli <100 microns in size. *Stroke* 34:1976-80.

## Basic

### Mark Ratcliffe, MD

*Staff Physician, Chief of Surgery, SFVAMC  
Associate Professor of Surgery, UCSF*

# Cardiac Ventricular Remodeling Surgery

**Dr. Ratcliffe was the first cardiac surgeon to use realistic mathematical models to evaluate the efficacy of novel surgical procedures for the treatment of heart failure and ischemic heart disease.** One evaluation was of the Myocor Myosplint, a device designed to change left ventricular (LV) shape and reduce heart wall stress. Regional wall stress cannot be measured in the intact heart, and LV function after surgical remodeling is often confounded by post-surgical medications and valve repair. Using a mathematical model, Dr. Ratcliffe found that Myosplint should be much more effective than partial ventriculectomy as a surgical therapy for patients with dilated cardiomyopathy and end-stage congestive heart failure. Dr. Ratcliffe also mathematically analyzed surgical anterior ventricular restoration (SAVER), another surgical treatment for heart failure, and determined the circumstances under which it can be used most effectively. **These studies will help surgeons develop surgical remodeling procedures that might decrease LV wall stress and improve LV function in heart failure patients.**

Guccione JM, Salahieh A, Moonly SM, Kortsmitt J, Wallace AW, Ratcliffe MB. 2003. Myosplint decreases wall stress without depressing function in the failing heart: a finite element model study. *Ann Thorac Surg* 76(4):1171-80.

Dang AB, Guccione JM, Zhang P, Wallace AW, Gorman RC, Gorman JH 3rd, Ratcliffe MB. 2005. Effect of ventricular size and patch stiffness in surgical anterior ventricular restoration: a finite element model study. *Ann Thorac Surg* 79(1):185-93.

## Basic

**Rajabrata Sarkar, MD, PhD**

*Staff Physician, Surgical Service, SFVAMC*

*Assistant Professor of Surgery, UCSF*

# Causes and Treatments of Blood Clots In the Leg

Each year, blood clots develop in the veins of over 2 million Americans and cause 200,000 deaths. **Dr. Sarkar's research focuses on the development and resolution of blood clots in the leg to identify how they cause scarring and thickening of the vein wall.** Clots can develop during pregnancy, following injuries, or after surgery, and cause both immediate and long-term problems. They can break off from the vein and travel to the lungs, a potentially fatal complication known as pulmonary embolism. Treatment with blood thinners prevents this dangerous complication, but does not prevent the long-term problems that lead to destruction of the valves and blockage within the leg veins, which can later lead to leg swelling, pain, and ulcers of the skin. How blood clots lead to these problems within the leg veins is not understood. Dr. Sarkar has developed an animal model of this condition and has identified a family of proteins (matrix metalloproteinases) which are potentially important in scarring and clot resolution. In addition, Dr. Sarkar has begun to study how the overexpression (excess production) of these proteins may potentially aid in the resolution of the blood clot. **This is the first step in developing a specific treatment to prevent long-term complications from blood clots in the vein.**

Dahi S, Lee JG, Lovett DH, Sarkar R. 2005. Differential transcriptional activation of matrix Metalloproteinase-2 and Membrane-Type 1 Matrix Metalloproteinase by experimental deep venous thrombosis and thrombin. *J Vasc Surg* (in press).



## Basic

### Norbert Schuff, PhD

*Senior Scientist, Radiology Service, SFVAMC  
Associate Professor of Radiology, UCSF*

# MRI for Diagnosis of Neurodegeneration

Dr. Schuff's research focuses on novel magnetic resonance imaging (MRI) techniques to detect structural, functional, and chemical changes in the brain during aging and in patients suffering from brain disorders such as Alzheimer's and Parkinson's disease. He showed that a **combination of imaging measurements that included structure, blood flow, and chemistry of the brain improved identification of subjects with age-related cognitive impairment, who are at increased risk for development of Alzheimer's disease.** Furthermore, Dr. Schuff is extending imaging studies to serial measurements to determine brain changes over time, especially to determine if MRI can detect effects of medical treatment for Alzheimer's disease. Dr. Schuff also applied MRI to study posttraumatic stress disorder (PTSD). **He found that PTSD was associated with reduction of certain neurochemicals in a brain region involved with memory function, suggesting a biological basis for the occurrence of PTSD.** More recently, Dr. Schuff has been focusing on developing a new MRI technique, termed arterial spin labeling MRI, to measure brain blood flow. Employing arterial spin labeling MRI to measure blood flow would be a substantial improvement for patient care, because MRI is more widely available, is non-invasive, and less expensive than the current standard method using positron emission tomography, which relies on injecting radioactive tracers.

Schuff N, Capizzano AA, Du AT, Amend DL, O'Neill J, Norman D, Jagust JW, Chui H, Kramer, Miller B, Yaffe K, Weiner MW 2003. Different patterns of N-acetylaspartate loss in ischemic vascular dementia and AD. *Neurology* 61:358-364.

Johnson NA, Jahng GH, Weiner MW, Miller BL, Chui HC, Jagust WJ, Gorno-Tempini ML, Schuff N. 2005. Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: initial experience. *Radiology* 234:851-9.



## Basic

**William Seaman, MD**

*Staff Physician, Chief of Immunology Section, SFVAMC  
Professor of Medicine and Microbiology/Immunology, UCSF*

# The Role of Ferritin & the Alliance for Cellular Signaling

Dr. Seaman studies ferritin, where iron is stored in the body in an inactive state until it is needed. The amount of ferritin in the blood goes up during infection, and ferritin can thus act as a signal that an infection is in progress. But how is the signal detected? Until now, this was unknown. Investigators in the laboratory of Dr. Seaman have identified, for the first time, a molecule on the surface of mouse cells that can detect ferritin. This molecule is expressed on immune cells, in the liver, and in the kidney. **This finding opens a new pathway to understanding the role of iron in health and disease.**

Dr. Seaman is also involved in the Alliance for Cellular Signaling, a group of eight laboratories in California, Texas, and Tennessee that have joined together to understand how each cell in the body responds to its environment. For example, how does a white blood cell know that there is an infection in progress and that it should activate its weapons to fight infection? Because no single laboratory has all of the expertise and technology to address this question, the Alliance combines and coordinates the expertise of its members to seek the answers. **It is a new way to do research that is highly collaborative and relies on technology to draw the investigators together (they meet regularly by televised conferences and put all of their results on a single computer).** Instead of waiting to publish their studies, the Alliance posts them on the Web, so that all scientists can access them for free. Other laboratories involved are at Stanford, Cal Tech, UC San Diego, the University of Texas Southwestern, and Vanderbilt. The San Francisco VAMC is the only VA to participate in the Alliance. The Alliance website is <<http://www.signaling-gateway.org>>.

Gilman AG, et al. 2002. Overview of the Alliance for Cellular Signaling. *Nature* 420:706.

Chen TT, Brown EJ, Huang EJ, Seaman WE. 2004. Expression and activation of signal regulatory protein alpha on astrocytomas. *Cancer Res* 64(1):117-27.



## Basic

### Dolores Shoback, MD

*Staff Physician, Medical Service, SFVAMC*

*Professor of Medicine, UCSF*

# Calcium Receptors in Bone Metabolism

**Dr. Shoback's laboratory is working on how specialized cells in the bone and bone marrow receive signals from the environment through receptors, how these signals are interpreted by cells in the bone and bone marrow, and how this affects the function of these cells.** She is testing the idea that calcium released from the bone mineral during bone breakdown, a process that occurs both normally and in disease states, alters the program of cell function and gene expression. Her work indicates that both bone-forming and bone-resorbing cells (osteoblasts and osteoclasts) respond to changes in extracellular calcium and that calcium itself is an important regulator of bone remodeling—a process that allows our skeleton to respond to exercise, disuse and hormonal activity. In her clinical research, she is working on multicenter clinical trials to test the efficacy of a newly developed drug (cinacalcet) to treat primary and secondary hyperparathyroidism. This drug is targeted to calcium receptors in the parathyroid glands. Primary hyperparathyroidism affects about 1 in 1000 people in the US, and causes blood calcium to rise and the content of mineral in bone to fall, leading to osteoporosis and other complications such as kidney stones. **She and her co-investigators have found that cinacalcet can normalize blood calcium in patients with primary hyperparathyroidism and maintain it at a normal level for up to 3 years.**

Chang W, Shoback D. 2004. Extracellular  $\text{Ca}^{2+}$ -sensing receptors - an overview. *Cell Calcium* 35:183-196.

Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D. 2005. Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endo Metab* 90:135-141.



## Basic

### Paul C. Simpson MD

*Staff Physician, Medical Service, SFVAMC*

*Professor of Medicine, UCSF*

# New Treatments for Heart Failure

Dr. Simpson is interested in discovering new drugs to treat heart failure, one of the most common causes of hospitalization and death in Veterans. To begin a basic science approach to this problem, Dr. Simpson in the 1980s **developed a new in vitro culture model, and used this model to show that a type of receptor for adrenalin had marked anabolic effects in heart muscle cells.** He has pursued this finding since, and recently discovered that mice lacking the key receptor develop heart failure. This finding correlates with clinical trials showing that blocking this receptor in human patients causes heart failure. Therefore, this basic research has two key implications for clinical practice. First, use of drugs that block these key receptors, a common practice in prostate disease, needs to be considered carefully. Second and conversely, activating this key receptor might be a new way to treat heart failure. Dr. Simpson is working now to test this novel idea.

Simpson P. 1983. Norepinephrine-stimulated hypertrophy of cultured rat myocardial cells is an alpha 1 adrenergic response. *J Clin Invest* 72:732-8.

O'Connell TD, Ishizaka S, Nakamura A, Swigart PM, Rodrigo MC, Simpson GL, Cotecchia S, Rokosh DG, Grossman W, Foster E, Simpson PC. 2003. The alpha(1A/C)- and alpha(1B)-adrenergic receptors are required for physiological cardiac hypertrophy in the double-knockout mouse. *J Clin Invest* 111:1783-91.



## Basic

**Paul M. Sullam, MD**

*Staff Physician, Medical Service, SFVAMC*

*Professor of Medicine, UCSF*

# Investigating Infective Endocarditis

Infective endocarditis is a life-threatening infection of the valves of the heart. Despite the use of antibiotics and surgical therapy, 20 to 25% of patients with this disease will die. A high percentage also develop major complications, such as stroke or heart failure. The population served by the VA contains a high proportion of persons at risk for endocarditis, such as patients with underlying rheumatic heart disease, a history of intravenous drug use, artificial cardiac valves, or pacemaker wires. The aim of Dr. Sullam's research is to define some of the basic mechanisms by which certain bacteria (streptococci and staphylococci) produce endocarditis. He is especially interested in determining how these microbes may attach to platelets, a type of blood cell that can be found on the surface of damaged or artificial heart valves. It is thought that this attachment of bacteria to the valves is the first step in producing infection. To date, Dr. Sullam **has identified several novel genes and proteins of these organisms that may mediate binding to platelets**. He is now in the process of determining just how these molecules produce binding, and what this means for the progression of infection. He hopes that this research will provide a basis for creating **new therapies or vaccines** to treat or prevent this serious, often fatal infectious disease.

Takamatsu D, Bensing BA, Sullam PM. 2004. Genes in the accessory sec locus of *Streptococcus gordonii* have three functionally distinct effects on the expression of the platelet binding protein GspB. *Mol Microbiol* 52:189- 203.

Takamatsu D, Bensing B, Sullam PM. 2005. Two additional components of the accessory Sec system mediating export off the *Streptococcus gordonii* platelet binding protein GspB. *J Bacteriol* 187:378-3883.



## Basic

### Raymond A. Swanson, MD

*Staff Physician, Chief of Neurology and Rehabilitation Service, SFVAMC  
Professor and Vice Chair of Neurology, UCSF*

# Hypoglycemic Brain Injury

The risk of hypoglycemia (low blood sugar) is the major factor limiting tight glucose control in patients with diabetes. Severe hypoglycemia causes coma and death of brain neurons. Research performed in Dr. Swanson's laboratory has established that the neuronal death resulting from hypoglycemia is not a straightforward result of energy failure, but results instead from a complex sequence of events initiated by hypoglycemia. Moreover, it is possible to intervene in this cell death pathway in order to prevent neuron death that would otherwise occur. This can be accomplished with a class of drugs known as PARP inhibitors. In a rat model of insulin-induced hypoglycemia, **PARP inhibitors were shown to prevent neuron death** when given as long as three hours after blood glucose correction. In the same rat model, **pyruvate, the form in which glucose is stored in cells, was found to be almost equally effective as the PARP inhibitors** in preventing hypoglycemic neuronal death. These studies suggest that patients who develop severe hypoglycemia can be treated with PARP inhibitors or pyruvate (in addition to glucose) to prevent hypoglycemic brain injury.

Suh SW, Aoyama K, Chen Y, Garnier P, Matsumori Y, Gum E, Liu J, Swanson RA. 2003. Hypoglycemic neuronal death and cognitive impairment are prevented by poly(ADP-ribose) polymerase inhibitors administered after hypoglycemia. *J Neurosci* 23:10681-90.

Suh SW, Aoyama K, Matsumori Y, Liu J, Swanson RA. 2005. Pyruvate administered after severe hypoglycemia reduces neuronal death and cognitive impairment. *Diabetes* 54:1452-8.



## Basic

**Donald A. Vessey, PhD**

*Career Scientist, Medical Research Service, SFVAMC  
Adjunct Professor of Biochemistry and Medicine, UCSF*

# Investigating Injury to the Heart from Loss of Blood Flow

The heart can be injured when its blood supply is reduced or cut off—a process known as ischemia—with the result that its ability to pump blood to the rest of the body may be severely impaired. One effect of ischemia is the death of heart muscle, commonly called a heart attack. Much of the damage to the heart occurs not during the actual period of ischemia, but when blood flow is reinitiated. This is termed reperfusion injury. Using rat models of ischemic heart disease, Dr. Vessey and his colleagues have found **that hearts can be protected from reperfusion injury through pretreatment with short, non-injurious cycles of ischemia.** This effect is referred to as preconditioning, and has **great potential for use in preventing various forms of reperfusion injury.** Dr. Vessey feels that his work will reveal an important component of this preconditioning effect, and thereby provide a method for chemically intervening to prevent damage to the heart muscle during recovery from ischemic heart disease.

Vessey DA, Kelley M, Karliner JS. 2005. A rapid assay sphingosine kinase. *Analytical Biochemistry* 337:136-142.



## Basic

**Maria L. Wei, MD, PhD**

*Staff Physician, Dermatology Service, SFGVAMC*

*Assistant Professor of Dermatology, UCSF*

# Diseases of Organelle Formation and Function

**Dr. Wei's laboratory studies multisystem diseases caused by single gene defects that result in organ failure due to dysfunction of organelles, which are structures with specialized functions within cells.** These diseases, Hermansky-Pudlak Syndrome, Chediak Higashi Syndrome, and Griscelli Syndrome, can cause premature death from pulmonary fibrosis, immunodeficiency, and neurological dysfunction. All of these syndromes share the clinical characteristics of prolonged bleeding and permanent vision disturbances as well as decreased pigmentation in the skin, hair, and eyes. Dr. Wei's laboratory studies cultured cells defective in the genes that cause these syndromes in order to determine the genes' cellular functions, identify the molecular mechanisms regulating organelle formation and function, and understand the underlying pathophysiology of these syndromes.

Nguyen T, Wei ML. 2004. Characterization of melanosomes in murine Hermansky-Pudlak Syndrome: Mechanisms of hypopigmentation. *J Invest Dermatol* 122(2):452.

Wei ML. 2005. Hermansky-Pudlak Syndrome: A disease of protein trafficking and organelle function. *Pigment Cell Res* (in press).

## Basic

**Michael W. Weiner, MD**

*Director of the Center for Imaging of Neurodegenerative Diseases, SFVAMC  
Professor of Radiology, Medicine, Psychiatry, and Neurology, UCSF*

# Advances in Diagnosing Brain Disorders using MRS and MRI

In 1980, Dr Weiner was **one of the first investigators to use nuclear magnetic resonance to investigate the metabolism of organs inside a living animal**. This technique subsequently became magnetic resonance spectroscopy—MRS—which is used together with MRI (magnetic resonance imaging). In 1988, Dr Weiner's group used MRS to show that the amino acid, N acetyl aspartate (NAA), a marker of healthy nerve cells, is reduced in the epileptic focus in the brain. This was confirmed by many other investigators and is now used to help identify the epileptic focus prior to surgery in epilepsy patients. In 1990, the group used MRS to show that NAA is also reduced in Alzheimer's disease. In 1994, they reported that NAA was reduced in the normal-appearing white matter of multiple sclerosis subjects; this finding suggested that MRS measurements of NAA were a much more sensitive measurement of disease than MRI. In 1998, Dr. Weiner et al. reported that NAA was reduced in the brains of patients with post-traumatic stress disorder (PTSD), emphasizing a biological role for this disease. Dr Weiner and his coworkers have reported that in patients with cognitive impairment and dementia due to strokes, the major predictor of impairment/dementia is the volume of brain gray matter. These observations have led to **a major change in the conceptualization of vascular dementia**, leading to improved diagnosis and treatment. In 2004, Dr. Weiner's group reported that reduced NAA predicts development of Alzheimer's disease in mildly impaired elderly subjects. They have also demonstrated that brain blood flow, measured with MRI, is reduced in Alzheimer's disease and in patients with mild impairment.

Kaiser LG, Schuff N, Cashdollar N, Weiner MW. 2005. Age-related glutamate and glutamine concentration changes in normal human brain: 1H MR spectroscopy study at 4 T. *Neurobiol Aging* 26(5):665-72.

Mueller SG, Laxer KD, Barakos JA, Cashdollar N, Flenniken DL, Vermathen P, Matson GB, Weiner MW. 2005. Metabolic characteristics of cortical malformations causing epilepsy. *J Neurol* Apr 29 (Epub ahead of print).



## Basic

### David Wofsy, MD

*Staff Physician, Chief of Arthritis/Immunology Section, SFVAMC  
Professor of Medicine and Microbiology/Immunology, UCSF*

# Treatment of Autoimmune Diseases with Monoclonal Antibodies & by Inhibition of T Cell Costimulation

Dr. Wofsy and his VA mentor Dr. William Seaman were the first investigators anywhere to use monoclonal antibodies to retard disease progression in mouse models for autoimmune diseases in humans. **Their pioneering work laid the foundation for the development of current monoclonal antibody therapies that have revolutionized treatment of several important rheumatic diseases in people, including rheumatoid arthritis, ankylosing spondylitis, juvenile arthritis, psoriasis and psoriatic arthritis.** This general approach to therapy has also shown promise in a host of other important diseases including diabetes mellitus, multiple sclerosis, systemic lupus, and systemic vasculitis.

Following his work with monoclonal antibodies, Dr. Wofsy examined the therapeutic effects of a protein designed to alter the function of T cells, the major cells that regulate immune function in health and disease. In these studies, he was the first to show that inhibition of T cell costimulation with a molecule designated CTLA4Ig could retard disease in mouse models for human autoimmune diseases. Since that time, CTLA4Ig has demonstrated promise in clinical trials in humans with psoriasis and with rheumatoid arthritis. **It is anticipated that CTLA4Ig will be approved by the FDA this year for treatment of rheumatoid arthritis.**

Wofsy D. 1991. Treatment of autoimmunity with monoclonal antibodies. In *Molecular Autoimmunity*. Talal N (ed), Academic Press, London, pp. 405-423.

Kalunian KC, Davis JC, Merrill JT, Totoritis MC, Wofsy D. 2002. Treatment of systemic lupus erythematosus by inhibition of T-cell costimulation with anti-CD154. *Arthritis Rheum* 46:3251-3258.



## Basic

**Joseph K. Wong, MD**

*Staff Physician, Medical Service, SFVAMC  
Associate Professor of Medicine, UCSF*

# HIV Persistence and Genetic Adaptability

**Dr. Wong was one of the first scientists to identify a small number of HIV-infected cells that can remain dormant in the bodies of patients receiving “cocktails” of antiviral drugs.** These cells have the ability to restart high levels of virus infection when antiviral drugs are stopped. Dr. Wong's laboratory now seeks to understand the nature of this form of dormant (latent) infection, as well as how low level replication of virus contributes to maintaining HIV in the body of patients, even after up to 10 years of continuous antiviral treatment. Such new information may help in the design of better ways of purging the last remnants of virus, and for refining existing ways we treat HIV-infected patients. Dr. Wong's laboratory has also worked with collaborators to better understand how HIV changes genetically to adapt to infection of cells in different body tissues. Because some antiviral drugs do not get into the brain, and up to 50% of untreated patients can develop central neurological complications that occur as a direct consequence of HIV infection, this is an important area of investigation. **Dr. Wong's laboratory was among the first to demonstrate the distinct genetic composition of HIV virus in the central nervous system, including those genetic elements that confer resistance to antiviral compounds.**

Strain MC, Gunthard HF, Havlir DV, Ignacio CC, Smith DM, Leigh-Brown AJ, Macaranas T, Lam RY, Daly OA, Fischer M, Opravil M, Levine H, Bachelier L, Spina CA, Richman D, Wong JK. 2003. Heterogeneous clearance rates of long-lived lymphocytes infected with HIV; intrinsic stability predicts lifelong persistence. *PNAS* 100:4819-4824.

Strain MC, Letendre S, Pillai S, Russell T, Ignacio C, Gunthard H, Good B, Smith D, Wolinsky S, Furtado M, Grant I, Ramns D, Marquie-Beck J, Durelle J, McCutchan JA, Ellis R, Wong JK. 2005. Genetic composition of HIV-1 in CSF and plasma without treatment and during failing antiretroviral therapy. *Virol* 79:1771-1788.



T. S. Benedict Yen, MD, PhD

*Staff Physician, Chief of Pathology, SFVAMC  
Professor and Vice Chair of Pathology, UCSF*

# Hepatitis B and C Viruses and Liver Injury

Dr. Yen's laboratory works on understanding how the hepatitis B and hepatitis C viruses cause disease. These are common and potentially deadly viruses that cause chronic injury to the liver, which can result in cirrhosis and liver cancer. **The rate of acute hepatitis B is four times greater in the VA system than in the general population, and the rate of hepatitis C is more than twice as great. It is estimated that more than 200,000 patients in the VA system have active hepatitis C.** Although liver transplantation can be a useful treatment for people with hepatitis B, some recipients will get a severe recurrent infection that rapidly leads to liver failure. The reason for this was unknown until **Dr. Yen's laboratory found a factor produced by the hepatitis B virus, named the large surface protein, that can directly injure the infected liver cell and cause cell death.** In hepatitis C patients, only 50 percent of those treated respond to current therapies, and thus new treatments are needed. Recently, **Dr. Yen's laboratory found that a protein factor in human liver cells called TIP47 is important for the hepatitis C virus to reproduce itself.** It is anticipated that these and other lines of research in Dr. Yen's laboratory will lead to new treatments for both viruses and hence improve the outlook for the many VA patients infected with these diseases.

Foo NC, Ahn BY, Ma X, Hyun W, Yen TSB. 2002. Cellular vacuolization and apoptosis induced by hepatitis B virus large surface protein. *Hepatology* 36:1400-1407.

Huang ZM, Tan T, Yoshida H, Mori K, Ma Y, Yen TS. 2005. Activation of hepatitis B virus S promoter by a cell type-restricted IRE1-dependent pathway induced by endoplasmic reticulum stress. *Mol Cell Biol* 25(17):7522-33.

## Basic

**Midori A. Yenari, MD**

*Staff Physician, Neurology Service, SFGVAMC  
Associate Professor of Neurology, UCSF*

# Cooling the Brain to Reduce Injury

It is well known that cooling the brain can reduce injury from conditions such as stroke and head trauma. However, the scientific reasons for this observation are not well known. Over the past few years, Dr. Yenari's lab has found that **therapeutic hypothermia (cooling the brain to 33° C) not only reduces the amount of injury after experimental stroke, but seems to do so through reducing inflammation at the genetic level**—that is, limiting the ability of brain cells to express genes involved in inflammation. Brain inflammation after stroke is known to worsen outcome. Since it is not practical to routinely cool all stroke patients, these results suggest that some stroke patients could benefit from anti-inflammatory therapy.

Han HS, Karabiyikoglu M, Kelly S, Sobel RA, Yenari MA. 2003. Mild hypothermia inhibits nuclear factor-kB translocation in experimental stroke. *J Cereb Blood Flow Metab* 23:589-598.

Deng H, Han HS, Cheng D, Sun GH, Yenari MA. 2003. Mild hypothermia inhibits inflammation following experimental stroke and brain inflammation. *Stroke* 34:2495-2501.



## Basic

**Weihai Ying, PhD**

*Research Biologist, Neurology Service, SFVAMC  
Assistant Adjunct Professor of Neurology, UCSF*

# Reducing Brain Cell Death and Injury & Slowing Aging

Prevention of neuronal death (death of brain cells) is essential for treatment of many devastating neurological diseases, including stroke, Parkinson's disease, traumatic brain injury, and diabetes. Dr. Ying's recent studies have focused on two enzymes, PARP-1 and PARG, both of which play a role in cell death associated with these conditions. He found that NADH, an important molecule in energy metabolism, can profoundly decrease PARP-1-mediated cell death. In addition, based on his research, several labs around the world have shown that inhibiting PARG can decrease ischemic injury (resulting from interruption of oxygen) to brains and several other organs. Both of these lines of research suggest potential new approaches for preventing and treating brain cell death. Finally, based on this research, **Dr. Ying has proposed that combined application of antioxidants, energy enhancing drugs, and calcium homeostasis-maintaining drugs may together decrease cell death in neurodegenerative diseases and slow the aging process.**

Alano C\*, Ying W\*, Swanson RA. 2004. NAD<sup>+</sup> depletion and mitochondrial permeability transition are required for poly(ADP-ribose) polymerase-1-induced cell death. *J Biol Chem* 279:18895-902.

\* Co-first author

Ying W, Alano CC, Garnier P, and Swanson RA. 2005. NAD<sup>+</sup> as a metabolic link between DNA damage and cell death. *J Neurosci Res* 79:216-23.



## Clinical

### Stephen Bent, MD

*Staff Physician, Medical Service, SFVAMC*

*Assistant Professor of Medicine, UCSF*

# Safety and Effectiveness of Herbal Remedies

Recent national surveys have shown that 20% of the population currently uses herbs to treat a medical illness or improve health. Since herbs and other dietary supplements do not require approval from the Food and Drug administration prior to marketing and sale, the safety of these products is not well established. Dr. Bent has conducted several projects to examine the **safety of herbal products**. A recent study found that the popular herb, **ephedra, was 40 times more dangerous than other herbal products**, and this work was cited by the FDA in their April, 2004 ban of ephedra. Dr. Bent's subsequent study examining an herb called citrus aurantium (which is now replacing ephedra in many "ephedra-free" products) found that this herb has no reliable evidence documenting either safety or efficacy. Dr. Bent has just completed a trial examining the efficacy of saw palmetto, an herb commonly used by men with enlarged prostates to improve their urinary symptoms (a very common condition among veterans). He has also applied for funding to study valerian (an herb used to improve insomnia) and mangosteen, a fruit believed to have efficacy in treating degenerative joint disease and arthritic pain.

Bent S, Tiedt TN, Odden M, Shlipak MG. 2003. The relative safety of ephedra compared with other commonly used herbs. *Ann Int Med* 138:468-471.



## Clinical

**Linda Chao, PhD**

*Assistant Research Scientist, Radiology Service, SFVAMC  
Associate Adjunct Professor of Radiology and Psychiatry, UCSF*

# Looking for Early Signs of Risk for Alzheimer's Disease

Over four million people in the United States have Alzheimer's disease. Although no medication slows the progression of the disease, a number of potential treatments are under development. **Dr. Chao has been using magnetic resonance imaging (MRI) to find signs that will help identify who may be at risk for developing Alzheimer's disease so that once an effective treatment does become available, we will know who should be treated.** Dr. Chao has been carrying out several investigations to better understand the changes in the brain that occur with normal and abnormal aging. She has been studying and comparing patterns of brain metabolism in cognitively impaired but non-demented older adults, cognitively normal older adults, and patients with Alzheimer's disease, and comparing patterns of metabolism with patterns of brain atrophy in the same populations. She has also been examining the relationship between concentrations of brain metabolites and performance on memory tests.

Du AT, Schuff N, Chao LL, Kornak J, Jagust WJ, Kramer JH, Reed BR, Miller BL, Norman D, Chui HC, Weiner MW. 2005. Age effects on atrophy rates of entorhinal cortex and hippocampus. *Neurobiol of Aging* 26:553-9.

Chao LL, Schuff N, Kramer JH, Du AT, Capizzano AA, O'Neill J, Wolkowitz OM, Jagust WJ, Chui HC, Miller BL, Yaffe K, Weiner MW. 2005. Reduced medial temporal lobe N-acetylaspartate in cognitively impaired but nondemented patients. *Neurology* 64(2):282-9.

## Clinical

**Kenneth Covinsky, MD, MPH**

*Staff Physician, Medical Service, SFVAMC*

*Associate Professor of Medicine, UCSF*

# Loss of Elders' Ability to Care for Themselves after Medical Hospitalization

Hospitalization is common in the elderly. Older people and their families frequently note that their health seems much worse after they are discharged from the hospital, even when the medical problem that led to hospitalization has been treated. Researchers at the SFVAMC have determined that these perceptions are valid. Dr. Covinsky assessed the ability of over 2000 patients to do basic self-care activities before and after hospitalization, including the ability to bathe, dress, transfer from a bed to a chair, use a toilet, and eat. Elders who can not do these activities without assistance can not live independently; they either require nursing homes or the help of a caregiver. Dr. Covinsky determined that over 1/3 of hospitalized elders had lost the ability to do at least one of these self-care activities by the time of hospital discharge. Among patients over age 85, over one-half lost the ability to do basic self care activities. These losses occurred even though most patients recovered from the acute medical problem that led to the hospitalization. There were two primary causes: failure to rehabilitate functional loss that occurred shortly before hospitalization, and failure to prevent new functional losses after hospital admission. **These results demonstrate that functional losses associated with hospitalization are a major source of disability in the elderly. This highlights the need to develop intervention strategies that minimize functional loss in hospitalized elders.**

Covinsky KE, Palmer RM, Fortinsky RH, Counsell SR, Stewart AL, Kresevic D, Burant CJ, Landefeld CS. 2003. Loss of independence in activities of daily living in older adults hospitalized with medical illness: Increased vulnerability with age. *J Am Geriatr Soc* 51:451-458.



## Clinical

**Bernard Dolan, OD, MS**

*Staff Physician, Surgical Service, SFVAMC  
Clinical Professor of Optometry, UC Berkeley*

# Vision Function with Posterior Capsular Opacification

After cataract surgery, many patients develop posterior capsular opacification—that is, the lens capsule left behind to support the implanted intraocular lens becomes cloudy. Dr. Dolan evaluated the effect of opacification on the patient's vision function. A series of vision test were performed on a group of patients with and without capsular opacification to determine the best test to use in evaluating patients with the condition. The results suggest that the best way to evaluate the impact of opacification on vision is to test vision using a chart with **low contrast letters** (gray rather than dark black), or to test the ability to see subtle **shades of gray under conditions of glare**.

Tuan K-MA, Bailey IL, Dolan BJ, Flach AJ. 2002. Visual functions assessment and posterior capsular opacification. *Invest Ophthalmol Vis Sci* 43:425.

## Clinical

**Deborah Grady, MD, MPH**

*Staff Physician, Medical Service, SFVAMC  
Professor of Epidemiology and Medicine, UCSF*

# Risks and Benefits of Postmenopausal Hormone Therapy

Dr. Grady is one of the world's leading experts on the risks and benefits of postmenopausal hormone therapy. In 1992, she developed evidence-based guidelines for use of postmenopausal hormone therapy for the American College of Physicians. With minor changes, these guidelines were adopted by the American College of Family Practice, the American Heart Association and the US Preventive Services Task Force. This work made it clear that if hormone therapy reduced the risk of coronary disease, it would be beneficial for most postmenopausal women, despite the likely increased risk of breast cancer. At this time, there were multiple observational studies demonstrating reduced risk of coronary disease among users compared to nonusers, but no evidence from a randomized trial. However, Dr. Grady and others felt that a randomized trial was imperative. She subsequently played a lead role in designing and conducting the Heart and Estrogen/progestin Replacement Study (HERS), the **first randomized trial of the effect of estrogen therapy on risk for heart disease events**. Surprisingly, this 20-center 7-year trial among 2763 postmenopausal women with coronary disease showed **no benefit of estrogen plus progestin therapy, and a 3-fold increased risk of blood clots**. Dr. Grady has also investigated the effect of postmenopausal hormone therapy on cognition, dementia, and a variety of other clinical outcomes, and written extensively on the rational clinical use of hormones.

Grady D, Wenger NK, Herrington D, Khan S, Furberg C, Hunninghake D, Vittinghoff E, Hulley S. 2000. Postmenopausal hormone therapy increases risk of deep vein thrombosis and pulmonary embolism: The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 132:689-96.

Grady D. 2003. Postmenopausal hormones -- therapy for symptoms only. *N Engl J Med* 348:1835-7.



## Clinical

**Carl Grunfeld, MD, PhD**

*Staff Physician, Chief of Metabolism and Endocrine Sections, SFVAMC  
Professor of Medicine, UCSF*

# Infection, Inflammation, and Atherosclerosis & HIV Complications

**A major cause of admission to VA hospitals is atherosclerosis. Dr. Grunfeld is the lead investigator in delineating how infection and inflammation can promote atherosclerosis.** He has shown that the body reacts to infection by changing how cholesterol and triglycerides travel in the blood. In the short run, these changes actually fight infection, but also promote atherosclerosis. Furthermore, when macrophages, the body's first line of host defense, are activated by infection or inflammatory signals, they turn into foam cells, the very first step in atherosclerosis.

**In HIV research, Dr. Grunfeld was the first researcher to propose that complications from protease inhibitors—insulin resistance, increased triglycerides and increased cholesterol—were not common to all protease inhibitors.** He demonstrated that some, but not all protease inhibitors induce insulin resistance, while others increase triglycerides and cholesterol. Given that the VA population of HIV-infected patients is aging, which predisposes to high triglycerides and diabetes, and that a large percentage were exposed to Agent Orange, which predisposes to diabetes, the knowledge gained from these studies can allow physicians to tailor their therapies to optimize outcomes. In addition, Dr. Grunfeld was the first to show that wasting in HIV was primarily due to the effects of opportunistic infections and failure to recover metabolically from those infections and not, as was thought, due to overwhelming replication of the virus. **His group went on to demonstrate that growth hormone could restore muscle mass and improve function in patients with HIV infection.**

Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, Grunfeld C. 2004. Effects of infection and inflammation on lipid metabolism: mechanisms and consequences to the host. *J Lipid Res* 45:1169-96.

Lee GA, Seneviratne T, Noor MA, Lo JC, Schwarz M, Aweeka FT, Mulligan K, Schambelan M, Grunfeld C. 2004. The metabolic effects of Lopinavir/ritonavir in HIV-negative men. *AIDS* 18:641-9.



## Clinical

### Kirsten Johansen, MD

*Staff Physician, Director of Dialysis, SFBVAMC*

*Associate Professor of Medicine, Epidemiology and Biostatistics, UCSF*

# Physical Activity in Patients on Dialysis

**Dr. Kirsten Johansen was one of the first investigators to perform detailed studies of physical functioning among dialysis patients, including physical performance, self-reported functioning, and muscle weakness and atrophy.** She was the first to quantify both the degree of physical inactivity among dialysis patients and the association between physical inactivity and mortality in this population. Dr. Johansen's group found that dialysis patients were significantly less active than even sedentary healthy individuals of similar age, and that physical inactivity is associated with higher mortality among patients on dialysis even after adjusting for other factors associated with inactivity and with mortality. In related research, Dr. Johansen designed and completed the first randomized study of the effects of anabolic steroids on lean body mass in dialysis patients. The study showed that patients who received nandrolone or decanoate for six months increased their lean body mass and improved their walking and stair-climbing compared to patients who received placebo injections. **A recent follow-up study—the largest randomized study of exercise or anabolic steroids in the dialysis population—showed that both nandrolone and weight lifting can increase leg muscle size, and that exercise also resulted in improvement in muscle strength and self-reported physical functioning.**

O'Hare AM, Tawney K, Bacchetti P, Johansen KL. 2003. Decreased survival among sedentary patients undergoing dialysis: Results from the Dialysis Morbidity and Mortality Study. *Am J Kidney Dis* 41(2):447-454.

Johansen KL, Doyle J, Sakka GK, Kent-Braun JA. 2005. Neural and Metabolic Mechanisms of Excessive Muscle Fatigue in Maintenance Hemodialysis Patients. *Am J Physiol Regul Integr Comp Physiol* 289:R805-13.

## Clinical

### Nick Kanas, MD

*Staff Physician, Associate Chief of Mental Health Service, SFVAMC  
Professor of Psychiatry, UCSF*

# People Under Stress and In Space

For the past 30 years, Dr. Kanas has studied the psychological interactions of people under stress and ways they can cope better with stressors in their environment. His earlier work involved groups of veteran patients suffering from alcoholism, PTSD, and schizophrenia. For the past 12 years, he has studied **astronauts living and working in space**. He has been the PI of two large NASA-funded international studies involving the Mir and International Space Stations, and he currently is the PI of a NASA-funded study aimed at training astronauts to deal with psychological stressors in space. In 1999, Dr. Kanas received the Aerospace Medical Association **Raymond F. Longacre Award for Outstanding Accomplishment in the Psychological and Psychiatric Aspects of Aerospace Medicine**. In 2003, Dr. Kanas received the **J. Elliott Royer Award for excellence in Academic Psychiatry**. Dr. Kanas is the co-author of a book entitled *Space Psychology and Psychiatry*, which was the recipient of the 2004 International Academy of Astronautics Life Sciences Book Award.

Kanas N. 1996. *Group Therapy for Schizophrenic Patients*. American Psychiatric Press, Washington, DC.

Kanas N, Manzey D. 2003. *Space Psychology and Psychiatry*. Kluwer Academic Publishers, Dordrecht, The Netherlands.



## Clinical

### Christopher J. Kane, MD, FACS

*Staff Physician, Chief of Urology, SFVAMC*

*Associate Professor of Urology, UCSF*

# Prostate Cancer Risk Assessment and Outcomes

Dr. Kane founded, along with five other investigators, the **Shared Equal Access Regional Cancer Hospital (SEARCH) database**. SEARCH is a compilation of retrospectively collected information on patients with prostate cancer who underwent radical prostatectomy at five VA Medical Centers and one Military Medical Center between 1990 to 2004. This is a unique database comprising an ethnically diverse population, cared for in equal-access medical centers. Using the detailed information on the over 2500 patients in the database, Dr. Kane and colleagues have been able to examine the impact of ethnicity, age, pretreatment prostate specific antigen levels, biopsy information, patient size, prostate size, pathologic stage and seminal vesicle invasion, among numerous other factors, on patient outcomes after radical prostatectomy. SFVAMC and Dr. Kane also participate in a large multicenter database of prostate cancer patients known as the CaPSURE database. Using this larger database including patients who have been treated at private medical facilities, Kane et al. have examined the differences between patients cared for in the VA Health Care system and explored **how patient demographics including educational level, obesity and comorbidities effect outcomes**.

Freedland SJ, Aronson WJ, Presti JC Jr., Amling CL, Terris MK, Trock B, and Kane CJ. 2004. Predictors of PSA progression among men with seminal vesicle invasion at the time of radical prostatectomy. *Cancer* 100:1633-1638.

Kane CJ, Bassett WW, Sadetsky N, Silva S, Wallace K, Pasta DJ, Cooperberg MR, Chan J, Carroll PR. 2005. Obesity and prostate cancer clinical risk factors at presentation, data from CaPSURE. *J Urol* 173:732-6.



## Clinical

### Edmund Keung, MD

*Staff Physician, Director of VA National ICD Surveillance Center, SFVAMC  
Associate Professor of Medicine, UCSF*

# Web-based Remote Monitoring of Internal Defibrillators

Internal cardioverter defibrillators (ICD) have been shown to be highly effective in improving overall mortality and preventing sudden cardiac death, which affects more than 400,000 patients annually. Recent technology enables remote transmission of comprehensive ICD performance and therapy history by telephone. In 2003, Dr. Keung applied for and received funding from VACO **to establish the National ICD Surveillance Center at SFVAMC** in order to offer this new leading-edge technology to all ICD patients and healthcare professionals in the VA Health Administration. Since establishment of the program, patient enrollment has already reached 3,000 from 80 VA facilities. It is the **largest remote ICD monitoring program in the world** and the first of its kind for any healthcare provider group. The VA has become the world leader in device remote monitoring. Utilization of VA facilities and patient travel time have been significantly reduced. The number of clinic visits has been reduced in some centers by as much as 75 percent, since patients can transmit their ICD data from home. This program has also provided an excellent example of how **clinical care and research can seamlessly work together to offer the best care for our veterans**. With the largest ICD database in the world, this research will help formulate ICD healthcare policy and enhance clinical care for the entire United States.

Davis N, Xue Y, Roberts L, Massie B, Keung E. 2005. Remote monitoring of implantable cardioverter defibrillators: Experience from the VA National ICD Surveillance Program. *Heart Rhythm* 2:S244.

Keung E, Xue Y. 2005. Remote Web-based Device Monitoring. *New Arrhythmia Technologies*, ed. P. Wang, Blackwell Publishing, Chapter 22 (in press).



## Clinical

**Young S. Kim, MD**

*Staff Physician, Medical Service, SFVAMC*

*Professor of Medicine, UCSF*

# Screening for Familial Colorectal Cancer

Colorectal cancer is the second most common cause of cancer death in the U.S. Advancing age and positive family history are important risk factors for this cancer. About 5% of colorectal cancer cases can be attributed to two genetic syndromes, familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). Another 20% of cases appear in patients with a positive family history of colorectal cancer but who do not have the genetic mutation associated with FAP or HNPCC. The development of cost effective and accurate screening methods for identifying individuals at high risk for developing colorectal cancer is the focus of research carried out by Dr. Kim and his colleagues. They have established the **first and largest familial colorectal cancer registry** in Northern California, consisting of over 500 families, and have provided genetic counseling, testing, and education. They also have analyzed a series of genetic and epigenetic abnormalities in colorectal cancer specimens obtained from patients with and without a family history and have determined factors that can distinguish the tumors of HNPCC patients from sporadic colorectal cancer patients. These pioneering studies have led to the **development of cost effective and accurate screening guidelines** for the diagnosis of patients with HNPCC, now widely adopted by the clinical and scientific communities.

Terdiman JP, Gum JR, Conrad PG, Miller GA, Weinberg V, Crawley SC, Levin TR, Reeves C, Schmitt A, Hepburn M, Sleisenger MH, Kim YS. 2001. Efficient detection of hereditary nonpolyposis colorectal cancer gene carriers by screening for tumor microsatellite instability before germline genetic testing. *Gastroenterology* 120:21-30.

Deng G, Bell I, Crawley S, Gum J, Terdiman JR, Allen B, Truta B, Sleisenger MH, Kim YS. 2004. BRAF mutation is frequently present in sporadic colorectal cancer with methylated hMLH1, but not in hereditary nonpolyposis colorectal cancer. *Clin Cancer Res* 10:191-195.



## Clinical

### Harry Lampiris, MD

*Staff Physician, Deputy Associate Chief of Staff for Clinical Research, SFVAMC  
Associate Professor of Medicine, UCSF*

# Clinical Trials for Infectious Diseases

**Dr. Harry Lampiris has been one of the lead investigators in the clinical development of new antiretroviral agents for HIV disease.** He has been involved in the phase 2 and 3 studies of many of the most important new antiretroviral agents in the last decade (lopinavir/ritonavir, tipranavir/ritonavir, enfuvirtide, tenofovir, TMC 114/ritonavir, and CCR-5 antagonists, for example), which affords veterans with HIV disease the access to these novel agents before they are FDA-approved. In addition, he has been actively involved in the development of new agents for nosocomial infections for gram-positive infections, particularly MRSA and VRE (linezolid and vancomycin).

DL Stevens, D. Herr, H. Lampiris JL Hunt, DH Batts, B Hafkin and the Linezolid MRSA Study Group. 2002. Linezolid versus vancomycin for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus*. *Clin Inf Dis* 34:1481-90.

RT Schooley, P Ruane, RA Myers, H Lampiris, D Berger, I McGowan, S Chen, MD Miller, E Isaacson, J Elder, A McCullough, A Cheng and the Study 902 Team. 2002. Tenofovir DF in highly antiretroviral-experienced patients: results from a 48 week, randomized, double blind study. *AIDS* 16:1257-63.



## Clinical

**Jialing Liu, PhD**

*Research Fellow, Surgical Service, SFVAMC  
Associate Professor of Neurological Surgery, UCSF*

# Nerve Cell Regeneration and Recovery from Stroke

There has been a lot of enthusiasm and hope in the stroke community since the **discovery of increased neurogenesis (nerve cell regeneration) following stroke reported by Dr. Jialing Liu and colleagues in 1998**. Numerous studies afterwards have confirmed the existence of post-stroke neuronal replacement at the sites of injury. Recently, Dr. Liu's group provided the **first evidence that stroke-induced neurogenesis might play a role in facilitating recovery of function in stroke patients**. Currently, Dr. Liu and colleagues are trying to enhance post-stroke functional recovery by promoting neurogenesis via either pharmacological or behavioral approaches. The information from her study is clinically relevant and important in the future development of post-stroke rehabilitation therapy.

Liu J, Solway K, Messing RO, and Sharp FR. 1998. Increased neurogenesis in the dentate gyrus after transient global ischemia in gerbils. *J. Neurosci* 18:7768-7778.

Raber J, Fang Y, Matsumori Y, Liu Z, Weinstein PR, Fike JR, Liu J. 2004. Irradiation attenuates neurogenesis and exacerbates ischemia-induced deficits. *Ann Neurol* 55:381-9.

## Clinical

**William J. Marks, Jr., MD**

*Staff Physician, Director of PADRECC, Neurology Service, SFVAMC  
Associate Professor of Neurology, UCSF*

# Brain Stimulation and Other Treatments for Parkinson's Disease

Parkinson's disease is a common condition caused by degeneration of brain cells in motor-controlling circuits of the brain. Medications help to control symptoms but reach a limit in their ability to provide patients with consistent, high quality motor function. Deep brain stimulation uses an implantable device to precisely deliver electrical impulses to key brain targets to override abnormal brain activity and bring motor circuits into a more normal state of function. This "pacemaker for the brain" alters the brain's activity (called neuromodulation) to suppress symptoms and enhance patients' function and quality of life. Dr. Marks has pioneered the use of deep brain stimulation for a variety of neurological conditions, especially Parkinson's disease. **SFVAMC was the first VAMC in the country to offer this treatment.** Dr. Marks and colleagues have evaluated a variety of issues pertaining to brain stimulation, including optimal surgical techniques and the merits of various brain targets. Other work at the SFVAMC focuses on the use of advanced neuroimaging techniques to evaluate patients with Parkinson's disease, sophisticated neurophysiological approaches to understand brain function in Parkinson's disease, and the use of a variety of pharmacological and interventional treatments for Parkinson's disease—including the world's first gene therapy trial using a growth factor to treat Parkinson's disease, which has recently been launched and may provide the ability to reverse disease progression and restore brain function.

Ostrem JL, Christine CW, Starr PA, Heath SL, Marks WJ Jr. 2004. Effect of patient age on response to subthalamic nucleus or globus pallidus deep brain stimulation for Parkinson's disease: results from a prospective, randomized study. *Neurology* 62:A396.

Marks WJ. 2005. Deep Brain Stimulation for Dystonia. *Curr Treat Opt Neurol* 7:237-243.



## Clinical

**Barry M. Massie, MD**

*Staff Physician, Chief of Cardiology Section, SFVAMC  
Professor of Medicine, UCSF*

# The Role of Anticoagulation and Antiplatelet Therapy in Treating Heart Failure

Dr. Massie and his colleagues conducted the Warfarin and Antiplatelet Trial in Chronic Heart Failure, a prospective randomized trial of three antithrombotic (anti-clotting) agents: warfarin or Coumadin, an anticoagulant; aspirin taken as an anticoagulant; and clopidogrel, an antiplatelet medication. The researchers studied 1588 patients with moderate to severe heart failure, with the goal of identifying the optimal agent with regard to efficacy and safety. With over 3,000 patient-years of follow-up, it represents the largest study of its kind to date. **There were no significant differences between the three agents in association with death, non-fatal myocardial infarction, non-fatal stroke, or mortality from all causes.** However, **there were significantly fewer strokes with warfarin than the antiplatelet agents.** In addition, **aspirin was associated with a significantly higher rate of worsening heart failure requiring hospitalization** compared to warfarin.

Massie BM, Krol WF, Ammon SE, et al. 2004. The Warfarin and Antiplatelet Therapy in Chronic Heart Failure trial (WATCH): rationale, design, and baseline patient characteristics. *J Card Fail* 10:101-12.

## Clinical

**David C. Mohr, PhD**

*Research Psychologist, Mental Health Service, SFGVAMC  
Associate Professor of Psychiatry, UCSF*

# Stress and MS Inflammation & Tele-Mental Health

Most patients with autoimmune diseases such as multiple sclerosis (MS) believe that stress causes exacerbations or relapses. **Dr. Mohr conducted the first study demonstrating that the occurrence of stressful life events leads to the development of new MS brain lesions eight weeks later.** He also found that treatments that reduce stress and distress are associated with a significant decline in T cell production of inflammatory proteins known to be lynchpins in the MS disease processes. He has begun the first trial of a stress management program aimed at reducing markers of brain inflammation.

Dr. Mohr is also a leading researcher in tele-mental health, or telephone administered psychotherapy. A large body of research has consistently shown that outcomes for mental health problems such as depression and anxiety are very poor. More than two-thirds of these patients would prefer psychotherapy to antidepressant medication, yet only 5-20% who receive referrals to specialty mental health care ever show up. Of those who show up, approximately half drop out of treatment. **Dr. Mohr is exploring telephone-administered psychotherapy as a method of overcoming barriers to mental health treatment.** He has found that such treatments are highly effective, achieve high satisfaction, and are associated with a low drop-out rate, usually under 10%.

Mohr DC, Likosky W, Dick LP, Van Der Wende J, Dwyer P, Bertagnolli D, Goodkin DE. 2000. Telephone-administered cognitive-behavioral therapy for the treatment of depressive symptoms in multiple sclerosis. *Consulting and Clin Psychol* 68:356-361.

Mohr DC, Hart SL, Julian L, Cox DC, Pelletier D. 2004. Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis and review. *BMJ* 328: 731-736.



## Clinical

### Thomas C. Neylan, MD

*Staff Physician, Medical Director of the Posttraumatic Stress Disorder Program, SFGVAMC  
Associate Professor of Psychiatry, UCSF*

# Stress Hormones and Insomnia in Veterans with PTSD

Dr. Neylan is studying the relationship of stress hormones and insomnia in veterans with Posttraumatic Stress Disorder (PTSD). **He has demonstrated that sleep disturbances are associated with high levels of the stress hormone cortisol, which has implications for the development of novel treatments for PTSD-related sleep disturbances.** In other work, Dr. Neylan recently completed the first controlled clinical trial of the blood pressure medication guanfacine in veterans with PTSD. Guanfacine and related medications are frequently recommended for the treatment of PTSD, and are in widespread use in VA PTSD clinics across the country. However, the results of this trial do not support the efficacy of this treatment, and demonstrate that guanfacine use is associated with a high rate of side effects. This study has implications for treatment of PTSD nationwide.

Otte C, Lenoci M, Metzler T, Yehuda R, Marmar CR, Neylan TC. 2005. Hypothalamus-pituitary-adrenal axis activity and sleep in posttraumatic stress disorder. *Neuropsychopharmacology* 30:1173-1180.

Neylan TC, Lenoci M, Franklin KW, Metzler TJ, Henn-Haase C, Hierholzer RW, Lindley SE, Otte C, Schoenfeld FB, Marmar CR. 2005. Guanfacine augmentation does not improve symptoms of Posttraumatic Stress Disorder. *Am J Psych* (in press).



## Clinical

**David Saloner, PhD**

*Director of the Vascular Imaging Research Center, SFVAMC*

*Professor of Radiology, UCSF*

# Imaging Vascular Disease

The Vascular Imaging Research Center (VIRC), directed by Dr. Saloner, has conducted studies that investigate the use of non-invasive Magnetic Resonance Imaging (MRI) methods for evaluating atherosclerotic disease. These methods provide the ability to identify and grade areas of vascular narrowing which pose a threat of a stroke to patients. The MRI methods are also able to **examine the composition of the disease process in the vessel wall, a capability that was not previously possible with other modalities**, and to identify important risk factors that are not apparent on other imaging methods. These methods avoid invasive arteriography, which has previously been the method of choice, providing a safer and more comprehensive evaluation for the large number of veterans who suffer from vascular disease. The VIRC team has also **developed new computational software capabilities that predict the influence of blood flow in the initiation and progression of disease**. This important capability is useful in gaining insight into factors that contribute to vascular disease, and strategies that can ameliorate that process.

Townsend TC, Saloner D, X.M. Pan XM, Rapp JH. 2003. Contrast material-enhanced MRA overestimates severity of carotid stenosis, compared with 3D time-of-flight MRA. *J Vasc Surg* 38:36-40.

Lorthois S, Stroud-Rossman J, Berger S, Jou L-D, Saloner D, 2005. Numerical simulation of Magnetic Resonance Angiographies of an anatomically realistic stenotic carotid bifurcation *Ann of Biomedical Eng* 33:270-83.



## Clinical

**Michael G. Shlipak, MD, MPH**

*Staff Physician, Chief of General Internal Medicine, SFVAMC*

*Associate Professor of Medicine, Epidemiology, and Biostatistics, UCSF*

# Using Kidney Function as A Predictor of Elder Cardiovascular Disease

Dr. Michael Shlipak was among the first investigators to demonstrate that **chronic kidney disease predicts cardiovascular disease progression and heart failure**, independent of standard risk factors. Currently, chronic kidney disease is clinically diagnosed by measurement of blood levels of the protein creatinine; the higher the level, the less efficient the kidney function. Dr. Shlipak's recent research has uncovered the potential of cystatin-C, a less commonly-measured blood protein, to more accurately reveal mild to moderate kidney impairment in the early, preclinical stages of chronic kidney disease. Dr. Shlipak and colleagues have shown **cystatin-C to be among the strongest predictors of cardiovascular disease, heart failure, and mortality risk in elderly persons**. This work demonstrates that the process of kidney disease begins prior to the clinical diagnosis of chronic kidney disease. Dr. Shlipak's work with cystatin-C was featured in the June 2005 edition of *VA Research Currents*.

Shlipak MG, Sarnak M, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS, Stehman-Breen CO. 2005. Cystatin-C and risk for mortality and cardiovascular disease in elderly adults. *N Engl J Med* 352(20):2049-60.

Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C, Bleyer A, Newman A, Siscovick D, Psaty B. 2005. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. *JAMA* 293:1737-45.



## Clinical

**Joel A. Simon, MD, MPH**

*Staff Physician, Medical Service, SFVAMC*

*Associate Professor of Clinical Medicine and Epidemiology and Biostatistics, UCSF*

# Smoking Cessation and the Epidemiology of Cardiovascular Disease

Dr. Simon has two related areas of research: the epidemiology of cardiovascular disease and smoking cessation, both of which are of vital importance to the health of veterans. He is also interested in the role of antioxidant nutrients and other dietary factors in the epidemiology of cardiovascular disease. **Dr. Simon is a nationally-recognized leader in smoking cessation research, and is involved in several studies investigating the effectiveness of different smoking cessation programs.** He is also co-principal investigator on a VA demonstration project, "VA in the Vanguard: Building on Success in Smoking Cessation." Dr. Simon is co-investigator on the Heart & Estrogen-progestin Replacement Study (HERS), a multi-year, multicenter study investigating coronary heart disease prevention in postmenopausal women. He is also co-principal investigator on a four-year project investigating the role of genetic variation in patient response to blood pressure and cholesterol-lowering medications.

Simon JA, Carmody TP, Hudes ES, Snyder E, Murray J. 2003. Intensive smoking cessation counseling versus minimal counseling among hospitalized smokers on transdermal nicotine replacement: a randomized trial. *Am J Med* 114:555-562.

Simon JA, Duncan C, Carmody TP, Hudes ES. 2004. Bupropion for smoking cessation: a randomized trial. *Arch Intern Med* 164:1797-1803.



## Clinical

**Phyllis C. Tien, MD**

*Staff Physician, Research Service, SFVAMC*

*Assistant Professor of Medicine, UCSF*

# Fat Distribution and Metabolic Changes in HIV Infection

Dr. Tien studies fat distribution and metabolic changes in HIV infection, particularly in women and in patients with HIV and hepatitis C virus coinfection. Fat distribution changes in HIV-infected patients were first reported in 1997, soon after the advent of highly active antiretroviral drugs to treat HIV. Dr. Tien established that in HIV-infected women, fat loss in both the peripheral body sites and the central body sites predominated when compared to HIV-uninfected women, and there was no difference in the amount of fat gain in the central body sites between HIV-infected and HIV-uninfected women. These important findings demonstrate that fat loss in both peripheral and central body sites are associated with HIV infection in women, and fat gain may be related to other factors such as aging. Dr. Tien is now studying fat changes that occur in patients infected with both HIV and hepatitis C. **Dr. Tien helped establish the SFVAMC HIV/Liver Clinic, which brings together HIV providers and hepatologists to provide an interdisciplinary approach to the care of patients infected with HIV and hepatitis viruses. She has also developed national VA guidelines for the management and treatment of hepatitis C in HIV-infected patients.**

Tien PC, Cole SR, Williams CM, Li R, Justman J, Cohen MH, Young M, Rubin N, Augenbraun M, Grunfeld C. 2003. Incidence of lipoatrophy and lipohypertrophy in the Women's Interagency HIV Study. *J AIDS* 34(5):461-466b.

Tien PC et al. 2005. Management and treatment of hepatitis C virus infection in HIV-infected adults: Recommendations from the Veterans Affairs Hepatitis C Resource Center Program and National Hepatitis C Program Office. *Am J Gastroenterol* (in press).



## Clinical

### Sophia Vinogradov, MD

*Staff Physician, Associate Chief of Mental Health for Research and Education, SFVAMC  
Professor of Psychiatry, UCSF*

# Schizophrenia and Mental Health

**Dr. Vinogradov studies how the brain malfunctions in schizophrenia, a devastating psychiatric illness that strikes young adults in their prime.** She is a co-investigator on a multi-site collaborative project that investigates the relationship between prenatal and early developmental factors and the later onset of schizophrenia. She is also a leader in the next wave of treatment and prevention of schizophrenia, using techniques of neuroscience-guided cognitive remediation: intensive computer-based training exercises to correct the brain information-processing abnormalities of the illness. Additionally, Dr. Vinogradov is working with senior researchers at UC Davis, UCLA, and UC San Diego to develop a consortium of programs that identify adolescents who show risk signs for developing schizophrenia and to intervene to prevent the illness.

Vinogradov S, Kirkland J, Poole JH, Drexler M, Ober BA, Shenaut GK. 2003. Both processing speed and semantic memory organization predict verbal fluency in schizophrenia. *Schizophr Res* 59(2-3):269-75.

Minzenberg MM, Poole JH, Fenton C, Vinogradov S. 2004. Evaluating anticholinergic effects on memory and complex attention in schizophrenia. *Am J Psych* 161:116-124.



## Clinical

### Paul Volberding, MD

*Staff Physician, Chief of Medicine, SFVAMC  
Professor and Vice-Chair of Medicine, UCSF*

# HIV/AIDS Treatment and Prevention

Dr. Volberding is world-renowned as one of the leading clinical researchers in the field of AIDS/HIV. Having led in defining the treatment for AIDS-related malignancies—Kaposi's sarcoma in particular—he **led or participated in most of the early pivotal trials of nucleoside analogs, the first AIDS drugs to be approved, and led the design of the first combination regimens of dual therapy for AIDS.** Today he works with leading researchers from around the world on HIV prevention and treatment. His interest in antiretroviral drugs continues, but he is also involved in studies investigating the **interactions of HIV/AIDS with other infections** and conditions including hepatitis, anemia, and AIDS-related malignancies and strategies for treating persons who are co-infected.

Gerbert B, Brown B, Volberding PA, Cooke M, Caspers N, Love C, Bronstone A. 1999. Physicians' transmission prevention assessment and counseling practices with their HIV-seropositive patients. *AIDS Education and Prevention* 11:307-320.

Chung RT, Anderson J, Volberding PA, Robbins GK, Lui T, Sherman KE, Peters MG, Koziel MJ, Alston B, Colquhoun D, Nevin T, Harb G, van der Horst C. 2004. A comparison of peg-interferon alfa-2A plus ribavirin vs. alfa-2A plus ribavirin for chronic hepatitis C virus infection in HIV-co-infected persons: The US clinical trials group A5071 study team. *N Engl J Med* 351:451-459.



## Clinical

**Arthur Wallace, MD, PhD**

*Staff Physician, Anesthesiology Service, SFVAMC*

*Associate Professor of Anesthesia and Perioperative Medicine, UCSF*

# Reducing Risks of Cardiac Surgery

Patients who have a history of coronary artery disease, peripheral vascular disease, or risk factors including hypertension, smoking, diabetes, elevated cholesterol, or age greater than 65 have a substantially increased risk of heart attack and death when they have major surgery. **Dr. Wallace demonstrated that the use of a beta blocker reduces the risk of death around the time of an operation by 50 – 90%, at a cost of less than \$20 per patient and less than \$600 per life saved.** Dr. Wallace then demonstrated that clonidine, a generic drug used to treat hypertension, also reduced the risk of death associated with surgery, potentially helping patients with asthma, electrical conduction problems in their hearts, or other risk factors associated with use of beta blockers. The use of beta blockers or clonidine around the time of surgery has not only reduced operative risk, it has changed the approach of cardiology to the surgical patient and dramatically reduced operative costs. **The use of beta blockers around the time of surgery has been adopted by the American Heart Association and American College of Cardiology for patients with coronary artery disease or peripheral vascular disease.**

Mangano DT, Layug EL, Wallace A, Tateo I, the Multicenter Study of Perioperative Ischemia (McSPI) Research Group. 1996. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Eng J Med* 335:1713–1720.

Wallace AW, Galindez D, Salahieh A, Layug B, Felipe EL, Haratonik K, Boisvert D, Kardatzke D. 2004. Effect of clonidine on cardiovascular morbidity and mortality after non-cardiac surgery. *Anesthesiology* 101: 284-293.



## Clinical

### Mary Whooley, MD

*Staff Physician, Medical Service, SFVAMC  
Associate Professor of Medicine, UCSF*

# The Mind-Heart Connection

Dr. Whooley's research is focused on detection and treatment of depression in patients with medical illness. In 1997, she developed a simple 2-question screening instrument to aid in the diagnosis of depression in medical patients. This simple instrument was immediately recognized as a tremendous improvement over the much longer (20-item) instruments that were previously available. **Over 70 VA medical centers, as well as numerous managed care organizations, now use the 2-question "Whooley depression screen"** to identify depression in primary care patients. In addition, the U.S. Preventive Services Task Force Guide to Clinical Preventive Services has referenced Dr. Whooley's work in recommending the use of shorter screening instruments for depression in primary care settings. Dr. Whooley has also demonstrated that **patients with depression are at increased risk for heart attacks and death from heart disease**. She designed her current project, the VA-funded Heart and Soul Study, to determine why patients with depression are at increased risk for heart disease. Since it began in 2000, almost 20 papers from the Heart and Soul Study have been published, including several in leading cardiology journals. Perhaps her most important paper compared the influence of depression and cardiac function on quality of life in patients with heart disease. Surprisingly, Dr. Whooley found that traditional measures of cardiac disease severity did not affect quality of life. These findings demonstrate that **efforts to improve quality of life should include greater emphasis on assessment and treatment of depression**. The ultimate goal of Dr. Whooley's work is to define specific target areas for improving the cardiovascular outcomes of depressed patients.

Odden MC, Whooley MA, Shlipak MG. 2004. Association of chronic kidney disease and anemia with physical capacity: The Heart and Soul Study. *J Am Soc Nephrology* 15:2908-2915.

McManus D, Pipkin S, Whooley M. 2005. Screening for depression in patients with coronary heart disease: Data from The Heart and Soul Study. *Am J Cardiology* (in press).



## Clinical

**Teresa L. Wright, MD**

*Staff Physician, Chief of Gastroenterology Section, SFVAMC  
Professor of Medicine, UCSF*

# Treatment of Hepatitis-C Infected Veterans & HIV/HCV Co-infection

**Under the leadership of Dr. Wright, the largest multicenter prospective screening, candidacy, and treatment study of veterans infected with hepatitis C was initiated.** This study has already produced several significant findings, including the fact that the majority of veterans—almost 60%—are not eligible for HCV treatment. Furthermore, of those eligible, only 44% actually initiated treatment, suggesting that additional supports may be required to improve eligibility and treatment enrollment of HCV-infected veterans. Due to the large number of African-American veterans in this study, Dr. Wright was able to assess whether African-American patients responded to treatment as well as non-African Americans. She found that African-American patients infected with HCV type GT-1 (but not GT-2 or -3) were found to have a lower treatment response, which could not be explained by dose reductions and other clinical laboratory data.

In other research, Dr. Wright was among the first to compare fatty liver disease in HCV/HIV versus HCV alone, and to study risk factors for fatty liver disease in co-infected patients. She found that patients infected only with HCV had more fatty liver disease than those co-infected with HCV and HIV; moreover, they were more obese, more likely to be diabetic, and had a higher alcohol intake. They were older than those with co-infection and were more likely to be engaged in risk behaviors. **These findings suggest that avoiding obesity and alcohol may benefit liver disease in patients with HCV/HIV co-infection, and points to the importance of avoiding profound immune deficiency by effective antiviral therapy.**

Currie S, Bini E, Shen H, Yee H, Wright T, for the VA-HCV-001 Study Group. 2005. Significant variation between HCV treatment acceptance and enrollment rates among sites in a large multicenter national study. *Digestive Diseases Weekly*, Chicago, USA.

Monto A, Dove LM, Bostrom A, Kakar S, Pien P, Wright TL. 2005. Hepatic steatosis in HIV-HCV coinfection: prevalence and significance compared to HCV mono-infection. *Hepatology* 42:310-316.



## Clinical

### Kristine Yaffe, MD

*Staff Physician, Chief of Geriatric Psychiatry, SFVAMC*

*Associate Professor of Psychiatry, Neurology and Epidemiology, UCSF*

# Cognitive Impairment, Dementia, Aging, and Health

Up to 50% of community-dwelling elderly individuals older than 85 years have dementia. Sixty to 98% also suffer from neuropsychiatric symptoms such as agitation, aggression, delusions, hallucinations, repetitive vocalizations, and wandering. Dr. Yaffe conducted a meta-analysis to evaluate the current drug treatment options for neuropsychiatric symptoms in dementia, and concluded that most are not effective due to side effects and low efficacy. **She developed a simple rubric that doctors can use to help decide which course of medication is appropriate.** This will hopefully guide physicians to the best use of medications and prevent older patients from being overmedicated.

In related research, Dr. Yaffe and colleagues conducted an international clinical trial of the drug raloxifene, which is commonly prescribed for osteoporosis, in a large sample of postmenopausal women. **They found that raloxifene reduced the risk of developing mild cognitive impairment by 33% among women—the first time an intervention has been shown to lower the risk of developing cognitive impairment or dementia.** Finally, Dr. Yaffe and colleagues performed a prospective analysis on patients who participated in voluntary health checks for 27 years, and found that people who were obese in mid-life were 74% more likely to develop dementia, while overweight people were 35% more likely to have dementia compared with those with normal weight. This is an important contribution to a body of literature urging for a healthier lifestyle and weight loss in the U.S.

Sink KM, Holden KF, Yaffe K. 2005. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA* 293:596-608.

Yaffe K, Krueger K, Cummings SR, Blackwell T, Henderson VW, Sarkar S, Ensrud K, Grady D. 2005. Effect of raloxifene on prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. *Am J Psych* 162:683-90.



## Clinical

### Judy Yee, MD

*Staff Physician, Chief of Radiology, SFVAMC*

*Associate Professor and Vice Chair of Radiology, UCSF*

# Virtual Colonoscopy

**Dr. Judy Yee was one of the first doctors to perform Virtual Colonoscopy (CT Colonography) not only in the VA system nationwide, but globally.** Virtual Colonoscopy is a new radiology test that uses a CT scanner and advanced computer software to create 3 dimensional pictures of the inside and outside of the colon that can be used to look for polyps that may develop into colon cancer. Virtual colonoscopy is **less invasive, safer, and less expensive** than the traditional way to screen for colon cancer which uses a long tube-like scope that is inserted throughout the colon. The VC test also allows the radiologist to look at organs outside of the colon. More patients who should be screened for colon cancer may actually come in for screening with the use of virtual colonoscopy. Dr. Yee has developed many of the innovative aspects of VC at the San Francisco VA to make this test more appealing to patients, and has published one of the largest studies showing excellent detection rates for VC. She has developed national guidelines for performing this test and has made a major contribution in how we screen for colon cancer.

Yee J, Akerkar GA, Hung RK, Steinauer-Gebauer AM, McQuaid K, Wall SD. 2001. Performance characteristics of CT colonography for the detection of colorectal neoplasia in 300 patients. *Radiology* 219:685-692.

Yee J, Kumar NN, Godara S, Casamina J, Hom R, Galdino G, Dell P, Liu D. 2005. Extracolonic Findings in a Male Population on CT Colonography. *Radiology* 236:519-526.



**Martha Buffum, DNSc, APRN, BC, CS**

*Associate Chief of Nursing Service for Research, SFVAMC*

*Associate Clinical Professor of Nursing, UCSF*

# Music to Reduce Pre-procedure Anxiety & Pain Assessment in Patients with Dementia

Patients' fear and anxiety prior to gastrointestinal exams (e.g. colonoscopy) and vascular angiography (e.g. angiograms) pose considerable nursing care challenges: reducing patients' discomfort, feelings of vulnerability and embarrassment, and fear about possible findings. Another result might be more difficult and painful procedures with greater need for sedating medication. **Dr. Buffum and colleagues have effectively reduced veterans' anxiety prior to GI procedures using music that veterans select. As a result of this study, the SFVAMC GI Diagnostic Center provides music to all patients undergoing procedures.** Dr. Buffum and colleagues are currently conducting a similar study in vascular angiography to reduce patients' anxiety prior to these procedures.

Dr. Buffum also studies pain in older adults with dementia, which is often overlooked because cognitive and communication deficits interfere with these patients' ability to verbalize their physical discomfort. Dr. Buffum and colleagues have tested methods for determining how patients with dementia demonstrate pain, and potential methods for relieving that pain. Further studies include determining nurses' pain evaluation methods for patients with dementia in all areas of the hospital, and learning family caregivers' descriptions of pain management of their loved ones when transferred from home to nursing homes and hospital settings. **These innovative studies are unique in the VA and show that persons with dementia should be evaluated for individual expression and treatment of pain and discomfort in all settings.**

Buffum M, Miaskowski C, Sands L, Brod M. 2001. A pilot study of the relationship between discomfort and agitation in patients with dementia. *Geriatric Nursing* 22:80-85.

Hayes A, Buffum M, Lanier E, Rodahl E, Sasso C. 2003. A music intervention to reduce anxiety prior to gastrointestinal procedures. *Gastroenterology Nursing* 26:145-149.



**William Byerley, MD**

*Staff Physician, Director of the Neurogenetics Substance Abuse Program, SFVAMC  
Professor of Psychiatry, UCSF*

## Links Between Genes and Mental Illness

The recent completion of the Human Genome Project has made gene discovery easier and more cost-effective. Dr. Byerley's laboratory is devoted to identifying genes that predispose to neuropsychiatric disorders such as schizophrenia and bipolar disorder, which together affect an estimated 2% of the world's population, and drug abuse. Dr. Byerley was an early leader in the field and has made important linkages between specific chromosomes and these disorders. His lab has examined genes underlying dopamine, serotonin, and other brain chemicals that play a role in behavior and personality. **Identification of genes will aid in the diagnosis and in the development of new drugs and treatments for these disorders.**

Cooper KC, Mesen A, Galke B, Delisi L, Byerley W. 2005. Suggestive linkage of schizophrenia to 5p13 in Costa Rica. *Mol Psychiatry* (7):651-6.

Klei L, Bacanu SA, Myles-Worsley M, Galke B, Xie W, Tiobech J, Otto C, Roeder K, Devlin B, Byerley W. 2005. Linkage analysis of a completely ascertained sample of familial schizophrenics and bipolars from Palau, Micronesia. *Human Genetics* (4):349-56.

**Mary-Margaret Chren, MD**

*Staff Physician, Dermatology Service, SFVAMC  
Associate Professor of Dermatology, UCSF*

# Improving Care for Skin Diseases by Measuring Patients' Quality of Life

Skin conditions affect many aspects of patients' well-being. They may cause substantial physical symptoms, dysfunction, and affect emotional health if they are disfiguring. Dr. Chren and her colleagues have developed a scientifically valid measure of the effects of skin diseases on quality of life called Skindex. **Skindex is now widely used in research studies as a measure of patient quality of life, and has been translated into over 10 languages.** Currently, Dr. Chren is using Skindex in a study of over 1500 patients with nonmelanoma skin cancer, the most common cancer. Initial data demonstrate that treatments for skin cancer differ in different practice settings, suggesting that physicians disagree about the best care for these common tumors, and highlighting the importance of the study to compare tumor recurrence and patient-reported outcomes after therapy.

Chren MM, Lasek RJ, Sahay AP, Sands LP. 2001. Measurement properties of Skindex-16, A brief quality-of-life measure for patients with skin diseases. *J Cutan Med Surg* 5:105-10.

Chren MM, Sahay AP, Sands LP, Maddock L, Lindquist K, Bertenthal D, Bacchetti P. 2004. Variation in care for nonmelanoma skin cancer in a private practice and a Veterans Affairs clinic. *Med Care* 42:1019-1026.

**Geon-Ho Jahng, PhD**

*Research Scientist, Radiology Service, SFVAMC  
Assistant Adjunct Professor of Radiology, UCSF*

# Novel Magnetic Resonance Imaging (MRI) Techniques to Measure Brain Blood Flow

Dr. Jahng's research focus is to develop and improve two relatively new methods that measure functional and physiological changes in brain disorders: arterial spin labeling (ASL) perfusion-MRI and diffusion tensor imaging (DTI)-MRI, and to apply these novel methods in the clinical setting. Clinicians can use these methods, which provide accurate measurement of blood flow in the brains of patients, to **better diagnose and treat diseases such as Alzheimer's**.

Jahng G-H, Zhu X-P, Matson GB, Weiner MW, Schuff N. 2003. Improved perfusion weighted MRI by a novel double inversion with proximal labeling of both tagged and control acquisitions. *Magn Reson Med* 49:307-314.

Jahng G-H, Song E, Zhu X-P, Matson GB, Weiner MW, Schuff N. 2005. Human brain: Reliability and reproducibility of pulsed arterial spin labeled perfusion MR imaging. *Radiology* 234:909-916.

**Sharad Jain, MD**

*Staff Physician, Assistant Chief of Medical Service, SFVAMC  
Associate Professor of Clinical Medicine, UCSF*

# Measuring Quality of Patient Care

Dr. Jain has been working with Dr. John Peabody to identify and develop methods to measure quality of patient care. **They have found that computerized clinical vignettes—online simulated patient consultations—accurately measure the care that is delivered by physicians in clinical practice.** Dr. Jain and Dr. Peabody are now using these vignettes to better understand how physicians treat common medical conditions in the outpatient setting. They are also working to identify ways to provide feedback to health care providers in order improve the care provided to patients. **Dr. Jain received the 2004 AAMC Humanism in Medicine award from the Association of American Medical Colleges (AAMC) and the Pfizer Medical Humanities Initiative. The award recognized Dr. Jain as a caring and compassionate mentor to medical students and as a physician who practices patient-centered medicine.**

Peabody JW, Luck J, Jain S, Bertenthal D, Glassman P. 2004. Assessing the accuracy of administrative data in health information systems. *Med Care* 42(11):1066-72.

Peabody JW, Luck J, Glassman P, Jain S, Hansen J, Spell M, Lee M. 2004. Measuring the quality of physician practice by using clinical vignettes: a prospective validation study. *Ann Intern Med* 141(10):771-80.

**Sara J. Knight, PhD**

*Staff Psychologist, Mental Health Service, SFVAMC  
Assistant Adjunct Professor of Psychiatry and Urology, UCSF*

# Patient Treatment Preferences and Health Outcomes

**Dr. Sara Knight's research aims to help veterans who come to the VA Health Care System make the best possible decisions about their health care and medical treatments.** One goal of this work is to improve physician understanding of veterans' needs, goals, and values when they are cared for in the VA. Her work has special relevance to the health care experiences of people who are poor and those who are from ethnic minority groups. Dr. Knight has developed and tested a program to help doctors provide better care for dying persons of different cultures. **She is among the first scientists to develop and evaluate practical and clinically useful measures of men's preferences for prostate cancer treatment,** validated for use with both black and white veterans and those of limited educational and economic resources.

Knight SJ, Siston AK, Chmiel J, Slimack N, Elstein A, Chapman G, Nadler R, Bennett CL. 2004. Ethnic variation in localized prostate cancer: A pilot study of preferences, optimism, and quality of life among black and white Veterans. *Clinical Prostate Cancer* 3:31-37.

Pickard AS, Knight SJ. 2005. Proxy evaluation of health-related quality of life: A conceptual framework for understanding multiple proxy perspectives. *Medical Care* 43:493-499.

**Seth Landefeld, MD**

*Staff Physician, Associate Chief of Staff of Geriatrics and Extended Care, SFVAMC  
Professor of Medicine, Epidemiology, and Biostatistics, UCSF*

## Improving Hospital Care

Dr. Landefeld and his colleagues invented the ACE (Acute Care for Elders) Unit and demonstrated its effectiveness in improving elders' ability to care for themselves and return home after hospitalization. The ACE Unit **restructured the way a medical ward works day-to-day**, bringing medical, nursing, and social work personnel together with patients and their family members in achieving **optimal outcomes of hospitalization**. ACE Units have been developed at approximately 100 acute hospitals across the country, including VAMCs. Dr. Landefeld and his colleagues have also identified common conditions as factors that contribute to disability and death after hospitalization, including cognitive impairment, depression, malnutrition, and difficulty paying for daily needs after leaving the hospital. These studies and others by Dr. Landefeld and his colleagues lay the foundation for studies to **reduce the risk and costs** of hospitalization, improving outcomes for patients and their families.

Landefeld CS, Palmer RM, Kresevic D, Fortinsky RH, Kowal J. 1995. A randomized trial of care in a hospital medical unit especially designed to improve the functional outcomes of acutely ill older patients. *N Engl J Med* 332:1338-1344.

Pierluissi E, Fischer MA, Campbell AR, Landefeld CS. 2003. Discussion of medical errors in Morbidity and Mortality Conference. *JAMA* 290: 2838-2842.

**Charles R. Marmar, MD**

*Staff Physician, Associate Chief of Staff of Mental Health, SFVAMC  
Professor and Vice Chair of Psychiatry, UCSF*

# Causes and Treatments of Posttraumatic Stress Disorder

**Dr. Marmar's research focuses on understanding and treating posttraumatic stress disorder (PTSD) in veterans, police officers and other emergency services personnel, terrorism survivors, and in accident and disaster victims.** He and his colleagues have found that PTSD is associated with specific markers in brain imaging and neuropsychological testing. In a study of 500 police academy recruits in the San Francisco Bay Area and New York, he found that childhood trauma exposure is related to greater reactivity to stress in adulthood. Dr. Marmar has consulted on training protocols for the United States Army casualty assistance and casualty notification units and the New York and London Metropolitan Police Departments, and is conducting research on 850 law enforcement officials in United States to determine the value of specific training in compassionate death notification practices. Currently, he is conducting a study exploring the value of building skills in emotion regulation as a promising strategy for helping veterans safely confront and master their combat memories in psychotherapy. **Dr. Marmar is beginning a study to determine if an approved, safe medication in combination with behavior therapy will accelerate recovery from combat PTSD in veterans returning from Afghanistan and Iraq.**

Neylan TC, Lenoci M, Rothlind J, Metzler TJ, Schuff N, Du AT, Franklin KW, Weiss DS, Weiner MW, Marmar CR. 2004. Attention, learning, and memory in posttraumatic stress disorder. *J Trauma Stress* 17(1):41-6.

Neylan TC, Brunet A, Pole N, Best SR, Metzler TJ, Yehuda R, Marmar CR. 2005. PTSD symptom predict waking salivary cortisol levels in police officers. *Psychoneuroendocrinology* 30(4):373-81.

**Barry M. Massie, MD**

*Staff Physician, Chief of Cardiology Section, SFVAMC  
Professor of Medicine, UCSF*

# Effects of Specialist and Nurse Practitioner Care on Outcomes and Treatments in Heart Failure Patients

Dr. Massie and his colleagues studied 405 patients with new onset chronic heart failure in order to determine whether patients who were seen by cardiac specialists within six months of diagnosis had better outcomes than those who were seen only by primary care practitioners (PCPs). **Patients with at least one visit to a cardiologist had a 38% lower risk of death or hospitalization than PCP-only patients over a 24 month period.** Another study looked at strategies for successfully treating heart failure patients with beta blockers, which are regularly received by less than 25% of patients even though they have been found to improve survival, reduce hospitalizations, and improve symptoms. **Dr. Massie and his colleagues found that 67% of patients assigned to doctors who worked with nurse facilitators were successfully started and maintained on beta blockers, compared with 16% of patients assigned to a computer reminder strategy and 27% of patients who received counseling and education.** Since clinical trials have indicated that one death is prevented for every 20 heart failure patients treated with beta blockers for one year, implementing the nurse practitioner strategy has potential major benefits. Currently, Dr. Massie and his research group are pursuing a strategy to encourage widespread use of the nurse practitioner approach.

Ansari M, Alexander M, Tutar A, Bello D, Massie BM. Cardiology participation improves outcomes in patients with new onset heart failure in the outpatient setting. 2003. *J Am Coll Cardiol* 41:62-8.

Ansari M, Shlipak MG, Heidenreich PA, Van Ostaeyen D, Browner W, Massie BM. 2003. Improving guideline adherence: A randomized trial evaluating strategies to improve beta-blocker use in heart failure. *Circulation* 107:1799-1804.

**Kala M. Mehta, PhD**

*Research Associate, Geriatric Service, SFVAMC*

*Assistant Adjunct Professor of Medicine and Geriatrics, UCSF*

## Geriatric Epidemiology

Dr. Mehta has shown that cognitive impairment and depressive symptoms leads to increased mortality rates among older adults. His work also established a clear link between these two conditions and what is known as functional decline, a worsening in a person's ability to complete a variety of everyday activities without assistance. These activities include such things as taking a bath or a shower, dressing, and eating. Using data from over 3,000 participants who were between 70 and 80 years old in the Health, Aging, and Body Composition (HABC) study, Mehta found that even among those without depression, anxiety symptoms are much more widespread among older adults than previous studies had uncovered. This had not been established before; this is important because it is known that anxiety is in itself debilitating. Using data from national databases, Mehta **applies state-of-the art statistical methodology to discover what makes older adults vulnerable to poor health** as they age.

Mehta KM, Yaffe K, Covinsky KE. 2002. Cognitive impairment, depressive symptoms and functional decline in the elderly. *Amer Geriatrics Soc* 50:1045-50.

Mehta KM, Yaffe K, Langa K, Sands L, Whooley M, Covinsky KE. 2003. Additive effects of cognitive function and depressive symptoms on mortality in older community living adults. *Gerontology: Medical Sciences* 58:M461-7.

**Sandra Moody-Ayers, MD**

*Staff Physician, Geriatrics Service, SFVAMC*

*Assistant Professor of Medicine and Geriatrics, UCSF*

# Health Disparities and End-of-Life Care

Dr. Moody-Ayers is recognized nationally for her work on health disparities. In her research, she uses large databases to understand the relationship between race/ethnicity and life-course socioeconomic status in relation to health outcomes in older and minority populations. She has shown that cognitive status is a powerful factor in explaining black-white disparities in functional decline among older persons. Her recent research has found **that childhood socioeconomic status influences health status in older age and is also a potential factor in racial-ethnic health disparities**. The next phase of her work will focus on aging, health disparities and end-of-life care. In particular, Dr. Moody-Ayers will examine the impact of sociocultural factors, including unfair treatment in society and in the medical system, on decision-making at the end of life in a cohort of multiethnic elders, particularly veterans.

Moody-Ayers S, Mehta K, Lindquist K, Sands L, Covinsky K. 2005. Black-white disparities in functional decline in older persons: The role of cognitive function. *J Gerontol A Biol Sci Med Sci* 60:933-939.

Moody-Ayers SY, Stewart AL, Covinsky KE, Inouye SK. 2005. Frequency of perceived societal racism among older African American Adults with type 2 diabetes mellitus. *J of Am Geriatr Soc* (in press).

Ann M. O'Hare, MA, MD

*Staff Physician, Medical Service, SFVAMC*

*Assistant Adjunct Professor of Medicine, UCSF*

# Peripheral Arterial Disease in Patients with Chronic Kidney Disease

Chronic kidney disease is a common condition affecting more than a half million veterans and more than 8 million Americans. People with kidney disease are at increased risk for cardiovascular events such as heart attack and stroke. Dr. O'Hare's research has shown that patients with chronic kidney disease are also more likely to have lower extremity circulatory disease (peripheral arterial disease), placing them at risk for amputation. She has also shown that **among veterans with peripheral arterial disease, chronic kidney disease is a powerful predictor of death.** Her ongoing research is intended to improve understanding of how to provide optimal care for patients with chronic kidney disease and peripheral arterial disease.

O'Hare AM, Glidden DV, Fox CS, Hsu CY. 2004. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999-2000. *Circulation* 109(3):320-3.

O'Hare AM, Bertenthal D, Shlipak MG, Sen S, Chren MM. 2005. Impact of renal insufficiency on mortality in advanced lower extremity peripheral arterial disease. *J Am Soc Nephrol*. 16(2):514-9.

**Jennifer B. Ritsher, PhD**

*Staff Psychologist, Mental Health Service, SFVAMC*

*Assistant Adjunct Professor of Psychiatry, UCSF*

# Internalized Stigma of Mental Illness

Dr. Ritsher's research investigates the influence of sociocultural factors on psychopathology and the effect of internalized stigma on the course of severe mental illness. When stigma is internalized, it contributes to a cycle of demoralization that works at cross-purposes with mental health treatment and impedes recovery. As a result, patients whose psychotic symptoms are resolved may still feel alienated from, and poorly integrated with, the community outside of the mental health treatment system. Dr. Ritsher found that even among patients with an average of over 25 years of mental illness, internalized stigma predicted further noticeable deterioration in morale (depressive symptoms and lowered self-esteem) over the course of just four months. Her Internalized Stigma of Mental Illness questionnaire has been translated into 6 languages and is being used in many projects around the world and across the US, as well as in several large-scale VA projects. Overall, Dr. Ritsher's research and clinical work supports the idea that **VA services that work against internalized stigma should help patients maximize their morale, mental illness coping skills, and community integration, and minimize their mental illness symptoms, substance use, and inpatient service use.**

Ritsher JB, Otilingam PO, Grajales M. 2003. Internalized stigma of mental illness: Psychometric properties of a new measure. *Psychiatry Research* 121:31-49.

Ritsher JB, Phelan J. 2004. Internalized stigma predicts erosion of morale among psychiatric outpatients. *Psychiatry Research* 129:257-265.

**Karen Seal, MD, MPH**

*Staff Physician, Medical Service, SFVAMC*

*Adjunct Assistant Professor of Medicine, UCSF*

# Investigating Medical Consequences of Substance Abuse

**Dr. Seal's work has been focused on the medical consequences of substance abuse, particularly injection drug use.** Past research endeavors include a randomized controlled trial demonstrating the effectiveness of cash incentives, as opposed to outreach, to enhance adherence to hepatitis B vaccine in injection drug users. Subsequently, Dr. Seal and colleagues demonstrated that training injection heroin users to use naloxone and CPR in the event of a heroin overdose would improve survival. Currently, Dr. Seal and her team are examining barriers to hepatitis C treatment for patients with substance use disorders and HIV coinfection. She is also conducting a secondary data analysis of a large national VA database of veterans with hepatitis C to explore whether veterans with substance use disorders are receiving the appropriate screening and clinical services for hepatitis C. **Recently, Dr. Seal has turned her attention to the potential problem of substance use disorders among veterans returning from Iraq and Afghanistan, particularly those veterans suffering from post-traumatic stress disorder and depression.** Finally, Dr. Seal is very interested in directly caring for patients with substance use disorders, helping them cope with medical problems incurred from substance use such as hepatitis C, and helping them enter substance use treatment.

Seal KH, Kral AH, Lorvick J, McNees A, Gee L, Edlin BR. 2003. A randomized controlled trial of monetary incentives vs. outreach to enhance adherence to the hepatitis B vaccine series among injection drug users. *Drug Alcohol Depend* 71(2):127-31.

Seal KH, Thawley R, Gee L, Bamberger J, Kral AH, Ciccarone D, Downing M, Edlin BR. 2005. Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: a pilot intervention study. *J Urban Health* (2):303-11.

**Saunak Sen, PhD**

*HSR&D Data Analysis Core, Research Service, SFVAMC  
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# Trawling the Data Seas: The Genome and Patient Databases

Databases have exploded since the advent of the information age. With advanced search tools, it is possible to retrieve individual data fragments such as a particular veteran's medical record or the DNA sequence of the hemoglobin gene. However, the knowledge hidden in the data ensemble is largely untapped. For example, we do not know what most of our genes do, even though we know the DNA sequence. **Dr. Sen has developed statistical methods for quantitative trait mapping which help determine the function of genes** by using crosses between animal strains (such as rats or mice). This technique is especially helpful to determine subtle genetic and gene-environment effects. He is also developing computational systems for statistical analysis of VA databases. **These systems provide objective information on how veterans are being cared for, and assess their unique needs.**

Sen S and Churchill GA. 2001. A statistical framework for quantitative trait mapping. *Genetics* 159:371-387.

Sen S, Satagopan JM, Churchill GA. 2005. Quantitative trait locus study design from an information perspective. *Genetics* 170:447-464.

**Michael Steinman, MD**

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*Assistant Professor of Medicine and Geriatrics, UCSF*

## Elders Who Restrict Use of Medication Due to Cost & Overuse of Broad-spectrum Antibiotics

Dr. Steinman, in association with SFVAMC researcher Dr. Kenneth Covinsky, conducted one of the first studies evaluating elderly Americans who restrict their own use of medications due to cost. **Dr. Steinman found that elders who lacked prescription drug coverage were substantially more likely to report having cut back on their use of medications due to cost than elders with this coverage.** Patients of minority ethnicity and those economically disadvantaged were at particularly high risk, with almost half of certain subgroups reporting having cut back on their medication use.

Dr. Steinman, in collaboration with SFVAMC Chief of Geriatrics Dr. Seth Landefeld and UCSF researcher Dr. Ralph Gonzales, also conducted two widely-publicized studies investigating the use and overuse of powerful broad-spectrum antibiotics in a national sample of community-based outpatient practices. **This research highlighted substantial overuse of broad-spectrum antibiotics**, both in conditions in which their use may be warranted, as well as in conditions where there is little justification for their use—a trend that is increasing over time. Dr. Steinman also found that physician specialty and region of the country were strongly associated with the choice of antibiotic, suggesting potential sources of unwanted variation.

Steinman MA, Sands LP, Covinsky KE. 2001. Medication restriction due to cost in seniors without prescription coverage: a national survey. *J Gen Intern Med* 16:793-99.

Steinman MA, Landefeld CS, Gonzales R. 2003. Predictors of broad-spectrum antibiotic prescribing for acute respiratory tract infections in adult primary care. *JAMA* 289:719-725.

**Louise C. Walter, MD**

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*Assistant Professor of Medicine, UCSF*

# Cancer Screening in Elderly Patients: A Framework for Individualized Decision-making

Dr. Walter became intrigued with learning about the risks and benefits of cancer screening in elderly patients because questions about when to stop screening arose frequently in her geriatrics clinic. Therefore, **she developed a conceptual framework to guide cancer screening decisions in older patients in a more sensible way.** First, she devised a method for estimating life expectancy and then developed a systematic approach that clinicians can use to weigh benefits and harms of screening based on an individual's estimated life expectancy and preferences. This framework was published in *JAMA* in 2001. **Since then, her framework has appeared in numerous cancer screening guidelines, such as the most recent American Cancer Society Guidelines.** Her framework is also widely used to teach decision-making in elderly patients in medical schools across the country.

Walter LC, Covinsky KE. 2001. Cancer screening in elderly patients: a framework for individualized decision making. *JAMA* 285:2750-2756.

Walter LC, Lindquist K, Covinsky KE. 2004. Relationship between health status and use of screening mammography and Papanicolaou smears among women older than 70 years of age. *Ann Intern Med* 140:681-688.